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(19) FEDERAL REPUBLIC OF GERMANY

GERMAN PATENT AND TRADEMARK OFFICE

(12) **Unexamined Patent Application**

(10) **DE 101 17 803 A 1**

(51) Int. Cl.[7]:
C 07 D 473/04
A 61 K 31/522

(21) Application No.: 101 17 803.4
(22) Filed: 10. 4. 2001
(43) Date Opened to Inspection: 24. 10. 2002

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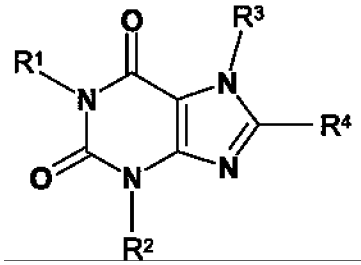
The following invention relates to substituted xanthines having the general formula

(54) Xanthine derivatives, their preparation and their use as medicinal products

(57) The following invention relates to substituted xanthines having the general formula



(I),

in which R^1 to R^4 are defined as in claim 1, the tautomers thereof, stereoisomers thereof, mixtures thereof, prodrugs thereof, and salts thereof that exhibit valuable pharmacological properties, in particular an inhibitory effect on the activity of the enzyme dipeptidyl peptidase-IV (DPP-IV).

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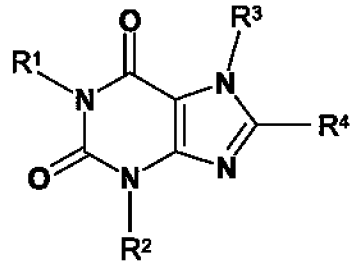
Description

[0001] The object of the present invention is substituted xanthines of the general formula



(I),

the tautomers thereof, the stereoisomers thereof, the mixtures thereof, and the salts thereof, in particular the physiologically compatible salts thereof with inorganic or organic acids or bases that have valuable pharmacological properties, in particular an inhibitory effect on the activity of the enzyme dipeptidyl peptidase-IV (DPP-IV), the preparation thereof, and the use thereof to prevent or treat diseases or conditions that are associated with an elevated DPP-IV activity or that can be prevented or mitigated through the reduction of DPP-IV activity, in particular of diabetes mellitus type I or type II, the medicinal products containing a compound of general formula I or a physiologically compatible salts thereof, as well as processes for their preparation.

[0002] The following meanings are used in a formula I above:

R^1 a hydrogen atom,

a C_{1-6}-alkyl group,

a C_{1-6}-alkyl group substituted by an R_a group, where

R_a means a C_{3-7} cycloalkyl, heteroaryl, cyano, carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl, pyrrolidine-1-ylcarbonyl, piperidine-1-ylcarbonyl, morpholine-4-ylcarbonyl, piperazine-1-ylcarbonyl, 4-methylpiperazine-1-ylcarbonyl, or 4-ethylpiperazine-1-ylcarbonyl group, a C_{1-6}-alkyl group substituted by a phenyl group, where the phenyl ring is substituted by the R^{10} to R^{14} groups, and

R^{10} means a hydrogen atom,

a fluorine, chlorine, bromine, or iodine atom,

a C_{1-3}-alkyl, hydroxy, or C_{1-3}-alkoxy group,

a nitro, amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)amino, pyrrolidine-1-yl, piperidine-1-yl, morpholine-4-yl, piperazine-1-yl, 4-(C_{1-3}-alkyl)-piperazine-1-yl, C_{1-3}-alkylcarbonylamino, arylcarbonylamino, aryl-C_{1-3}-alkylcarbonylamino, C_{1-3}-alkyloxycarbonylamino, C_{1-3}-alkylsulfonylamino, arylsulfonylamino, or aryl C_{1-3}-alkylsulfonylamino group,

a N-(C_{1-3}-alkyl)-C_{1-3}-alkylcarbonylamino, N-(C_{1-3}-alkyl)-arylcarbonylamino, N-(C_{1-3}-alkyl)-aryl-C_{1-3}-alkylcarbonylamino, N-(C_{1-3}-alkyl)-C_{1-3}-alkyloxycarbonylamino, N-(C_{1-3}-alkyl)-C_{1-3}-alkylsulfonylamino, N-(C_{1-3}-alkyl)-arylsulfonylamino, or N-(C_{1-3}-alkyl)-aryl-C_{1-3}-alkylsulfonylamino group,

a cyano, carboxy, C_{1-3}-alkyloxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl, pyrrolidine-1-yl-carbonyl, piperidine-1-yl-carbonyl, morpholine-4-yl-carbonyl, piperazine-1-yl-carbonyl, or 4-(C_{1-3}-alkyl)-piperazine-1-yl-carbonyl group,

a C_{1-3}-alkylcarbonyl, or an arylcarbonyl group,

a carboxy-C_{1-3}-alkyl, C_{1-3}-alkyloxycarbonyl-C_{1-3}-alkyl, cyano-C_{1-3}-alkyl, aminocarbonyl-C_{1-3}-alkyl, C_{1-3}-alkylaminocarbonyl-C_{1-3}-alkyl, di-(C_{1-3}-alkyl)-aminocarbonyl-C_{1-3}-alkyl, pyrrolidine-1-yl-carbonyl-C_{1-3}-alkyl, piperidine-1-yl-carbonyl-C_{1-3}-alkyl, morpholine-4-yl-carbonyl-C_{1-3}-alkyl, piperazine-1-yl-carbonyl-C_{1-3}-alkyl, or 4-(C_{1-3}-alkyl)-piperazine-1-yl-carbonyl-C_{1-3}-alkyl group,

a carboxy-C_{1-3}-alkyloxy, C_{1-3}-akyloxycarbonyl-C_{1-3}-alkyloxy, cyano-C_{1-3}-alkyloxy, aminocarbonyl-C_{1-3}-alkyloxy, C_{1-3}-alkylaminocarbonyl-C-$_{1-3}$-alkyloxy, di-(C_{1-3}-alkyl)-aminocarbonyl-C_{1-3}-alkyloxy, pyrrolidine-1-yl-carbonyl-C_{1-3}-alkyloxy, piperidine-1-yl-carbonyl-C_{1-3}-alkyloxy, morpholine-4-yl-carbonyl-C_{1-3}-alkyloxy, piperazine-1-ylcarbonyl-C_{1-3}-alkyloxy, or 4-(C_{1-3}-alkyl-)-piperazine-1-yl-carbonyl-C_{1-3}-alkyloxy group,

a hydroxy-C_{1-3}-alkyl, C_{1-3}-alkoxy-C_{1-3} alkyl, amino-C_{1-3}-alkyl, C_{1-3}-alkylamino C_{1-3}-alkyl, di-(C_{1-3}-alkyl)-amino-C_{1-3}-alkyl, pyrrolidine-1-yl-C_{1-3}-alkyl, piperidine-1-yl-C_{1-3}-alkyl, morpholine-4-yl-C_{1-3}-alkyl, piperazine-1-yl-C_{1-3}-alkyl, 4-(C_{1-3}-alkyl)-piperazine-1-yl-C_{1-3}-alkyl group,

a hydroxy-C_{1-3}-alkyloxy, C_{1-3}-alkoxy-C_{1-3} alkyloxy, amino-C_{1-3}-alkyloxy, C_{1-3} alkylamino-C_{1-3}-alkyloxy, di-(C_{1-3}-alkyl)-amino-C_{1-3}-alkyloxy, pyrrolidine-1-yl C_{1-3}-alkyloxy, piperidine-1-yl-C_{1-3}-alkyloxy, morpholine-4-yl-C_{1-3}-alkyloxy, piperazine-1-yl-C_{1-3}-alkyloxy, 4-(C_{1-3}-alkyl)-piperazine-1-yl-C_{1-3}-alkyloxy group,

a mercapto, C_{1-3}-alkylsulfenyl, C_{1-3}-alkysulfinyl, C_{1-3}-alkylsulfonyl, C_{1-3}-alkylsulfonyloxy, trifluoromethylsulfenyl, trifluoromethylsulfinyl, or trifluoromethylsulfonyl group,

a sulfo, aminosulfonyl, C_{1-3}-alkylaminosulfonyl, di-(C_{1-3}-alkyl)-aminosulfonyl, pyrrolidine-1-yl-sulfonyl, piperidine-1-yl-sulfonyl, morpholine-4-yl-sulfonyl, piperazine-1-yl-sulfonyl, or 4-(C_{1-3}-alkyl)-piperazine-1-yl-sulfonyl group,

a methyl, or methoxy group substituted to 1 to 3 fluorine atoms,

an ethyl, or ethoxy group substituted by 1 to 5 fluorine atoms,

a C_{2-4}-alkenyl or C_{2-4}-alkinyl group,

a 2-propene-1-yloxy or 2-propyne-1-yloxy group,

a C_{3-6}-cycloalkyl or C_{3-6}-cycloalkoxy group,

a C_{3-6}-cycloalkyl-C_{1-3}-alkyl or C_{3-6}-cycloalkyl-C_{1-3}-alkoxy group, or
an aryl, aryloxy, aryl-C_{1-3}-alkyl, or aryl-C_{1-3}-alkoxy group,
R^{11} and R^{12}, which may be identical or different, each mean a hydrogen atom, a fluorine, chlorine, bromine, or iodine atom, a C_{1-3}-alkyl, trifluoromethyl, hydroxy, or C_{1-3}-alkoxy group, or a cyano group, or
R^{11} together with R^{12}, if they are attached to adjacent carbon atoms, also mean a methylenedioxy, linear C_{3-5}-alkylene, -CH=CH-CH=CH-, -CH=CH-CH=N-, or -CH=CH-N=CH- group, and
R^{13} and R^{14}, which may be identical or different, each mean a hydrogen atom, a fluorine, chlorine, or bromine atom, a trifluoromethyl, C_{1-3}-alkyl, or C_{1-3}-alkoxy group,
a C_{2-6}-alkyl group substituted by a R_b group, where
R^b is isolated from the ring nitrogen by at least two carbon atoms, and
R_b means a hydroxy, C_{1-3}-alkoxy, amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl), pyrrolidine-1-yl, piperidine-1-yl, morpholine-4-yl, piperazine-1-yl, 4-methylpiperazine-1-yl, or 4-ethylpiperazine-1-yl group,
a C_{3-6}-cycloalkyl group, or
a C_{3-4}-alkenyl, or C_{3-4}-alkinyl group, where the multiple bond is isolated from the ring nitrogen by at least one carbon atom,
R^2 means a hydrogen atom,
a C_{1-6}-alkyl group,
C_{1-6}-alkyl group substituted by a phenyl group, where the phenyl ring is substituted by the groups R^{10} to R^{14}, and R^{10} to R^{14} are defined as stated above,
a C_{1-6}-alkyl group substituted by an R_a group, where
R_a means a C_{3-7}-cycloalkyl, heteroaryl, cyano, carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl, or di-(C_{1-3}-alkyl)-aminocarbonyl, pyrrolidine-1-ylcarbonyl, piperidine-1-ylcarbonyl, morpholine-4-ylcarbonyl, piperazine-1-ylcarbonyl, 4-methylpiperazine-1-ylcarbonyl, or 4-ethylpiperazine-1-ylcarbonyl group, a C_{2-6}-alkyl group substituted by an R_b group, where
R_b is isolated from the ring nitrogen by at least two carbon atoms, and
R_b means a hydroxy, C_{1-3}-alkoxy, amino, C_{1-3}-alkylamino, or di-(C_{1-3}-alkyl)-amino, pyrrolidine-1-yl, piperidine-1-yl, morpholine-4-yl, piperazine-1-yl, 4-methylpiperazine-1-yl, or 4-ethylpiperazine-1-yl group,
a C_{3-6}-cycloalkyl group, or
a C_{3-4}-alkenyl, or C_{3-4}-alkinyl group, where the multiple bond is isolated from the ring nitrogen by at least one carbon atom,
R^3 means a C_{1-6}-alkyl group,
a C_{1-6}-alkyl group substituted by an R_c group, where
R_c means a C_{3-7}-cycloalkyl group that is optionally substituted by a C_{1-3}-alkyl group,
a C_{5-7}-cycloalkenyl group that is optionally substituted by a C_{1-3}-alkyl group, or
an aryl or heteroaryl group,
a linear or branched C_{3-8}-alkenyl group, in which the double bond is isolated from the ring nitrogen by at least one carbon atom,
linear or branched C_{3-6}-alkenyl group substituted by a chlorine, or bromine add-on, an aryl, or trifluoromethyl group, in which the double bond is isolated from the ring nitrogen by at least one carbon atom,
or a linear or branched C_{3-6}-alkinyl group, in which the triple bond is isolated from the ring nitrogen by a least one carbon atom, and
R^4 means an azetidine-1-yl or pyrrolidine-1-yl group, that is substituted in the 3-position by a R_eNR_d group and that may also be substituted by one or two C_{1-3}-alkyl groups, where
R_e means a hydrogen atom or a C_{1-3}-alkyl group, and
R_d means a hydrogen atom, a C_{1-3}-alkyl group, a R_f-C_{1-3}-alkyl group, or a R_g-C_{2-3}-alkyl group, where
R_f means a carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl, pyrrolidine-1-ylcarbonyl, 2-cyanopyrrolidine-1-yl-carbonyl, 2-carboxypyrrolidine-1-yl-carbonyl, 2-methoxycarbonylpyrrolidine-1-ylcarbonyl, 2-ethoxycarbonylpyrrolidine-1-yl-carbonyl, 2-aminocarbonylpyrrolidine-1-yl-carbonyl, 4-cyanothiazolidine-3-yl-carbonyl, 4-carboxythiazolidine-3-ylcarbonyl, 4-methoxycarbonylthiazolidine-3-yl-carbonyl, 4-ethoxycarbonylthiazolidine-3-yl-carbonyl, 4-aminocarbonylthiazolidine-3-yl-carbonyl, piperidine-1-yl-carbonyl, morpholine-4-ylcarbonyl, piperazine-1-ylcarbonyl, 4-methylpiperazine-1-ylcarbonyl, or 4-ethylpiperazine-1-ylcarbonyl group, and
R_g, which is separated from the nitrogen atom of the R_eNR_d-by at least two carbon atoms, means a hydroxy, methoxy, or ethoxy group,
a piperidine-1-yl or hexahydroazepine-1-yl group, that is substituted in the 3-position or in the 4-position by a R_eNR_d-group and that may also be substituted by one or two C_{1-3}-alkyl groups, where R_e and R_d are defined as stated above,
a piperidine-1-yl or hexahydroazepin-1-yl- group that is substituted in the 3-position by an amino, C_{1-3}-alkylamino, or di-(C_{1-3}-alkyl)-amino group, in which in each case two hydrogen atoms are replaced on the carbon backbone of the piperidine-1-yl or hexahydroazepin-1-yl- group by a linear alkylene bridge, were said bridge contains 2 to 5 carbon atoms if the two hydrogen atoms are located on the same carbon atom, or 1 to 4 carbon atoms if the hydrogen atoms are located at adjacent carbon atoms, or 1 to 4 carbon atoms if the hydrogen atoms are located on carbon atoms that are separated by one atom, or it contains 1 to 3 carbon atoms if the two hydrogen atoms are located on carbon atoms that are separated by two atoms,
a C_{3-7}-cycloalkyl group substituted by an amino, C_{1-3}-alkylamino, or di-(C_{1-3}-alkyl)-amino group,

a C_{3-7}-cycloalkylamino, or N-(C1–3-alkyl)-C3–7-cycloalkylamino group substituted in the cycloalkyl part by an amino, C_{1-3}-alkylamino, or di-(C_{1-3}-alkyl)-amino group, where the two nitrogen atoms on the cycloalkyl part are separated from each other by least two carbon atoms,
an amino group substituted by the remainders R^{15} and R^{16}, in which
R^{15} represents a C_{1-6}-alkyl group, a C_{3-6}-cycloalkyl, C_{3-6}-cycloalkyl-C_{1-3}-alkyl, aryl, or aryl-C_{1-3}-alkyl group, and
R^{16} represents an R^{17}-C_{2-3}-alkyl group, where the C_{2-3}-alkyl part is linear and may be substituted by one to four C_{1-3}-alkyl groups, which may be identical or different, and
R^{17} represents an amino, C_{1-3}-alkylamino, or di-(C_{1-3}-alkyl)-amino group, where, if R^3 means a methyl group, R^{17} must not represent a di-(C_{1-3}-alkyl)-amino group,
an amino group substituted by the remainders R^{15} and R^{18}, in which
R^{15} is defined as stated above, and R^{18} represents a C_{3-6}-cycloalkylmethyl group that is substituted in the 1-position of the cycloalkyl remainder by R^{19}, or a C_{3-6}-cycloalkyl group that is substituted in the 1-position by an R^{19}-CH_2- group, where R^{19} represents an amino, C_{1-3}-alkylamino, or di-(C_{1-3}-alkyl)-amino group,
an amino group that is substituted by the remainders R^{15} and R^{20}, in which
R^{15} is defined as stated above and R^{20} represents an azetidine-3-yl, azetidine-2-ylmethyl, azetidine-3-ylmethyl, pyrrolidine-3-yl, pyrrolidine-2-ylmethyl, pyrrolidine-3-ylmethyl, piperidine-3-yl, piperidine-4-ylmethyl, piperidine-2-ylmethyl, or piperidine-4-ylmethyl group, where remainders referred to for R^{20} may each be substituted by one or two C_{1-3}-alkyl groups,
an R^{17}-C_{3-4}-alkyl group, in which the C_{3-4}-alkyl part is linear and is substituted by the remainder R^{15} and may also be substituted by one or two C_{1-3}-alkyl groups, where R^{15} and R^{17} are defined as stated above, a C_{3-6}-cycloalkyl-CH_2CH_2- group substituted in the 1- position of the cycloalkyl remainder by R^{19}, a C_{3-6}-cycloalkyl-CH_2 group substituted in the 1-position of the cycloalkyl remainder by an R^{19}-CH_2 group, or a C_{3-6}-cycloalkyl group substituted in the 1-position by an R^{19}-CH_2CH_2 group, where R^{19} is defined as stated above,
a C_{3-6}-cycloalkylmethyl group substituted in the 2-position of the cycloalkyl remainder R^{19} or a C_{3-6}-cycloalkyl group substituted in the 2-position by an R^{19}-CH_2- group, where R^{19} is defined as stated above,
or an azetidine-2-yl-C_{1-2}-alkyl, azetidine-3-yl-C_{1-2}-alkyl, pyrrolidine-2-yl-C_{1-2}-alkyl, pyrrolidine-3-yl, pyrrolidine-3-yl-C_{1-2}-alkyl, piperidine-2-yl-C_{1-2}-alkyl, piperidine-3-yl, piperidine-3-yl-C_{1-2}-alkyl, piperidine-4-yl, or piperidine-4-yl-C_{1-2}-alkyl group, where the groups referred to above may each be substituted by one or two C_{1-3}-alkyl groups,
where the aryl groups referred to in the definition of the residues cited above are understood to mean phenyl groups that may be mono- or disubstituted independently of each other by R_h mono, where the substituents may be identical or different, and R_h represents a fluorine, chlorine, bromine, or iodine atom, a trifluoromethyl, C_{1-3}-alkyl, or C_{1-3}-alkoxy group,
where the heteroaryl groups referred to in the definition of the residues cited above are understood to mean a 5-member heteroaromatic group that contains an imino group, an oxygen or sulfur atom, or an imino group, an oxygen or sulfur atom, and one or two nitrogen atoms, or
they are understood to mean a 6-member heteroaromatic group that contains 1, 2, or three nitrogen atoms
where the 5-member heteroaromatic groups cited above may each be substituted by one or two C_{1-3}-alkyl groups, and the 6-member heteroaromatic groups cited above may each be substituted by one or two C_{1-3}-alkyl groups or by a fluorine, chlorine, bromine, or iodine atom, by a trifluoromethyl, hydroxy, or by a C_{1-3}-alkoxy group,
the isomers and the salts thereof.

[0003] The carboxyl groups referred to in the definition of the remainders stated above may be substituted by a group that may be converted in-vivo into a carboxy group or by a group that is negatively charged under physiological conditions, and, moreover, the amino and imino groups referred to in the definition of the remainders stated above may be substituted by a remainder that can be cleaved off in-vivo. Such groups are described, for example, in WO 98/46576 and by N. M. Nielsen et al. in International Journal of Pharmaceutics 39, 75-85 (1987).

[0004] A group that can be converted in-vivo to a carboxy group, for example a hydroxymethyl group, is understood to mean a carboxy group that is esterified with an alcohol, in which the alcoholic part preferably is a C_{1-6}-alkanol, a phenyl-C_{1-3}-alkanol, a C_{3-9}-cycloalkanol, where a C_{5-8}-cycloalkanol is additionally substituted by one or two C_{1-3}-alkyl groups, a C_{5-8}-cycloalkanol, in which a methylene group group in the 3- or 4-position may be substituted by oxygen atom or by an imino group, which may be substituted by a C_{1-3}-alkyl, phenyl-C_{1-3}-alkyl, phenyl-C_{1-3}-alkoxycarbonyl, or C_{2-6}-alkanoyl group, and the cycloalkenyl part may also be substituted by C_{1-3}-alkyl groups, a C_{4-7}-cycloalkenol, a C_{3-5}-alkenol, a phenyl-C_{3-5}-alkenol, a C_{3-5}-alkinol, or phenyl-C_{3-5}-alkinol with the stipulation that no bond to the oxygen atom may begin at a carbon atom that has a double or triple bond, a C_{3-8}-cycloalkyl-C_{1-3}-alkanol, a bicycloalkanol having a total of 8 to 10 carbon atoms, that in the bicycloalkyl part may also be substituted by one or two C_{1-3}-alkyl groups, a 1,3-dihydro-3-oxo-1-isobenzfuranol or in alcohol having the formula

R_p-CO-O-(R_qCR_r)-OH,

in which
R_p represent a C_{1-8}-alkyl, C_{5-7}-cycloalkyl, C_{1-8}-alkyloxy, C_{5-7}-cycloalkyloxy, phenyl, or phenyl- C_{1-3}-alkyl group, R_q represents a hydrogen atom, a C_{1-3}-alkyl, C_{5-7}-cycloalkyl, or phenyl group, and
R_r represents a hydrogen atom or a C_{1-3}-alkyl group,
a group that is negatively charged under physiological conditions is understood to be a tetrazol-5-yl, phenylcarbonylaminocarbonyl, trifluoromethylcarbonylaminocarbonyl, C_{1-6}-alkylsulfonylamino, phenylsulfonylamino, benzylsulfonylamino, trifluoromethylsulfonylamino, C_{1-6}-alkylsulfonylaminocarbonyl, phenylsulfonylaminocarbonyl, benzylsulfonylaminocarbonyl, or

perfluoro-C_{1-6}-alkylsulfonylaminocarbonyl group and a remainder that is understood to be able to be cleaved off in-vivo from an imino or amino group is understood to be, for example, a hydroxy group, an acyl group such as a phenylcarbonyl group that in some cases may be substituted by fluorine, chlorine, bromine, or iodine atoms, by C_{1-3}-alkyl, or C_{1-3}-alkoxy groups , where the substituents may be identical or different, a pyridinoyl group or a C_{1-16}-alkanoyl group such as the formyl, acetyl, propionyl, butanoyl, pentanoyl, or hexanoyl group, a 3,3,3-trichloropropionyl, or allyloxycarbonyl group, a C_{1-16}-alkoxycarbonyl, or C_{1-16}-alkylcarbonyloxy group, in which hydrogen atoms may be completely or partially replaced by fluorine or chlorine atoms, such as the methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl- tert.-butoxycarbonyl, pentoxycarbonyl, hexoxycarbonyl, octyloxycarbonyl, nonyloxycarbonyl, decyloxycarbonyl, undecyloxycarbonyl, dodecyloxycarbonyl- hexadecyloxycarbonyl, methylcarbonyloxy, ethylcarbonyloxy, 2,2,2-trichloroethylcarbonyloxy, propylcarbonyloxy, isopropylcarbonyloxy, butylcarbonyloxy, tert.-butylcarbonyloxy, pentylcarbonyloxy, hexylcarbonyloxy, octylcarbonyloxy, nonylcarbonyloxy, decylcarbonyloxy, undecylcarbonyloxy, dodecylcarbonyloxy, or hexadecylcarbonyloxy group, a phenyl-C_{1-6}-alkoxycarbonyl group such as the benzyloxycarbonyl, phenylethoxycarbonyl, or phenylpropoxycarbonyl group, a 3-aminopropionyl group, in which the amino group is mono or is substituted by C_{1-6}-alkyl, or C_{3-7}-cycloalkyl groups, entity substituents may be identical or different, a C_{1-3}-alkylsulfonyl-C_{2-4}-alkoxycarbonyl, C_{1-3}-alkoxy-C_{2-4}-alkoxy-C_{2-4}-alkoxycarbonyl, R_p-CO-O-(R_qCR_r)O-CO, C_{1-6}-alkyl-CO-NH-(R_sCR_t)-O-CO, or C_{1-6}-alkyl-CO-O-(R_sCR_t)-(R_sCR_t)-O-CO group, in which R_p to R_r are defined as stated above,

R_s and R_t, which may be identical or different, represent hydrogen atoms or C_{1-3}-alkyl groups.

[0005] Furthermore, the saturated alkyl and alkoxy parts that are referred to in the previous and following definitions and that contain more than 2 carbon atoms, also include their branched isomers, such as the isopropyl, tert.-butyl, isobutyl group.

[0006] R^1 and R^2 may, for example mean a hydrogen atom, a methyl, ethyl, propyl, 2-propyl, butyl, 2-butyl, 2-methylpropyl, 2-propene-1-yl, 2-propyne-1-yl, cyclopropylmethyl, benzyl, 2-phenylethyl, 3-phenylpropyl, 2-hydroxyethyl, 2-methoxyethyl, 2-ethoxyethyl, 2-(dimethylamino)ethyl, 2-(diethylamino)ethyl, 2-(pyrrolidineo)ethyl, 2-(piperidineo)ethyl, 2-(morpholineo)ethyl, 2-(piperazineo)ethyl, 2-(4-methylpiperazino)ethyl, 3-hydroxypropyl, 3-methoxypropyl, 3-ethoxypropyl, 3-(dimethylamino)propyl, 3-(diethylamino)propyl, 3-(pyrrolidineo)propyl, 3-(piperidineo)propyl, 3-(morpholineo)propyl- 3-(piperazineo)-propyl, 3-(4-methylpiperazino)propyl, carboxymethyl, (methoxycarbonyl)methyl, (ethoxycarbonyl)methyl, 2-carboxyethyl, 2-(methoxycarbonyl)ethyl, 2-(ethoxycarbonyl)ethyl, 3-carboxypropyl, 3-(methoxycarbonyl)propyl, 3-(ethoxycarbonyl)-propyl, (aminocarbonyl)methyl, (methylaminocarbonyl)methyl, (dimethylaminocarbonyl)methyl, (pyrrolidineocarbonyl)methyl, (piperidineocarbonyl)methyl, (morpholineocarbonyl)methyl, 2-(aminocarbonyl)methyl, 2-(methylaminocarbonyl)ethyl, 2-(dimethylaminocarbonyl)ethyl, 2-(pyrrolidineocarbonyl)ethyl, 2-(piperidineocarbonyl)-ethyl, 2-(morpholineocarbonyl)ethyl, cyanomethyl, or 2-cyanoethyl group.

[0007] R_3 may, for example, mean a methyl, ethyl, propyl, 2-propyl, butyl, 2-butyl, 2-methylpropyl, pentyl, 2-methylbutyl, 3-methylbutyl, 2,2-dimethylpropyl, cyclopropylmethyl, (1-methylcyclopropyl)methyl, (2-methylcyclopropyl)methyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, 2-(cyclopropyl)ethyl,

2-propene-1-yl, 2-methyl-2-propene-1-yl, 3-phenyl-2-propene-1-yl, 2-butene-1-yl, 4,4,4-trifluoro-2-butene-1-yl, 3-butene-1-yl, 2-chloro-2-butene-1-yl, 2-bromo-2-butene-1-yl, 3-chloro-2-butene-1-yl, 3-bromo-2-butene-1-yl, 2-methyl-2-butene-1-yl, 3 -methyl-2-butene-1 -yl, 2,3-dimethyl-2-butene-1-yl, 3-trifluoromethyl-2-butene-1-yl, 3-methyl-3-butene-1-yl, 1-cyclopenten-1-ylmethyl, (2-methyl-1-cyclopenten-1-yl)methyl, 1-cyclohexen-1-ylmethyl, 2-(1-cyclopenten-1-yl)ethyl, 2-propyne-1-yl, 2-butyne-1-yl, 3-butyne-1-yl, benzyl, a fluorobenzyl, chlorobenzyl, bromobenzyl, methylbenzyl, methoxybenzyl, 1-phenylethyl, 2-phenylethyl, 3-phenylpropyl, 2-furanylmethyl, 3-furanylmethyl, 2-thienylmethyl, or 3-thienylmethyl group.

[0008] R^4 may, for example, mean a 3-aminopyrrolidine-1-yl, 3-aminopiperidine-1-yl, 3-(methylamino)-piperidine-1-yl, 3-(ethylamino)-piperidine-1-yl, 3 -(dimethylamino)-piperidine-1-yl, 3 -(diethylamino)-piperidine-l-yl, 3-[(2-hydroxyethyl)-amino]-piperidine-l-yl,

3-[N-methyl-N-(2-hydroxyethyl)-amino]-piperidine-1-yl, 3-[(3-hydroxypropyl)amino]-piperidine-1-yl, 3-[N-methyl-N-(3-hydroxypropyl)-amino]-piperidine-1-yl, 3-[(carboxymethyl) amino]-piperidine-1-yl, 3-[(methoxycarbonylmethy)amino]-piperidine-1-yl, 3-[(ethoxycarbonylmethy)amino]-piperidine-1-yl, 3-[N-methyl-N-(methoxycarbonylmethyl)-amino]-piperidine-1-yl, 3-[N-methyl-N-(ethoxycarbonylmethyl)-amino]piperidine-1-yl, 3-[(2-carboxyethyl)-amino]-piperidine-1-yl, 3-{[2-(methoxycarbonyl)ethyl]amino}-piperidine-1-yl, 3-{[2-(ethoxycarbonyl)ethyl]amino}-piperidine-1-yl, 3-(N-methyl-N-[2-(methoxycarbonyl)ethyl]-amino)-piperidine-1-yl, 3-{N-methyl-N-[2-(ethoxycarbonyl)ethyl]-aminopiperidine-1-yl, 3-[(aminocarbonylmethyl)amino]-piperidine-1-yl, 3-[(methylaminocarbonylmethyl)amino]-piperidine-1-yl, 3-[(dimethylaminocarbonylmethyl)-amino]-piperidine-1-yl, 3-[(ethylaminocarbonylmethyl)amino]-piperidine-1-yl, 3-[(diethylaminocarbonylmethyl)amino]-piperidine-1-yl, 3-[(pyrrolidine-1 ylcarbonylmethyl)amino]-piperidine-1-yl, 3-[(2-cyanopyrrolidine-1-ylcarbonylmethyl) amino]piperidine-1 -yl, 3-[(4-cyanothiazolidine-3-ylcarbonylmethyl)amino]-piperidine-1-yl, 3-[(2-aminocarbonylpyrrolidine-1-ylcarbonylmethyl)amino]-piperidine-1-yl, 3-[(2-carboxypyrrolidine-1-yl-carbonylmethyl)amino]-piperidine-1-yl, 3-[(2-methoxycarbonylpyrrolidine-1-ylcarbonylmethy)amino]-piperidine-1-yl, 3-[(2-ethoxycarbonylpyrrolidine-1-ylcarbonylmethyl)-amino]-piperidine-1-yl, 3-[(piperidine-1-ylcarbonylmethyl)amino]-piperidine-1-yl, 3-[(morpholine-4-ylcarbonylmethy)amino]-piperidine-1-yl, 3-amino-2-methyl-piperidine-1-yl, 3-amino-3-methyl-piperidine-1-yl, 3-amino-4-methyl-piperidine-1-yl, 3-amino-5-methyl-piperidine-1-yl, 3-amino-6-methyl-piperidine-1-yl, 2-amino-8-aza-bicyclo[3.2.1]oct-8-yl, 6-amino-2-aza-bicyclo[2.2.2]oct-2-yl, 4-aminopiperidine-1-yl, 3-aminohexahydroazepin-1-yl, 4-aminohexahydroazepin-1-yl, 3-aminocyclopentyl, 3-aminocyclohexyl, 3-(methylamino)-cyclohexyl, 3-(ethylamino)-cyclohexyl,

3-(dimethylamino)-cyclohexyl, 3-(diethylamino)-cyclohexyl, 4-aminocyclohexyl, (2-aminocyclopropyl)amino, (2-aminocyclobutyl)amino, (3-aminocyclobutyl)amino, (2-aminocyclopentyl)amino, (3-aminocyclopentyl)amino, (2-aminocyclohexyl)amino, or (3-aminocyclohexyl)amino group.

[0009] Preferred compounds of general formula I above are those in which

R^1 means a hydrogen atom,
a C_{1-4}-alkyl group,
a C_{1-4}-alkyl group substituted by an R_a group, where
R_a means a C_{3-6}-cycloalkyl or a phenyl group,
a C_{2-4}-alkyl group terminally substituted by an R_b group, where
R_b represents a hydroxy, C_{1-3}-alkoxy, amino, C_{1-3}-alkylamino, or di-(C_{1-3}-alkyl)-amino group,
or a C_{3-4}-alkenyl, or C_{3-4}-alkinyl group, where the multiple bond is isolated from the ring nitrogen atom by at least one carbon atom,
R^2 means a hydrogen atom or a C_{1-3}-alkyl group,
R^3 means a C_{1-3}-alkyl group terminally substituted by the R_c group, where
R_c means a C_{5-6}-cycloalkenyl group,
a phenyl group optionally substituted by a fluorine, chlorine, or bromine atom, by a C_{1-3}-alkyl or C_{1-3}-alkoxy group, or
a furanyl, or thienyl group,
a linear or branched C_{3-6}-alkenyl group, in which the double bond is isolated from the ring nitrogen atom by at least one carbon atom,
or a linear or branched C_{3-6}-alkinyl group, in which the triple bond is isolated from the ring nitrogen by a least one carbon atom, and
R^4 means a pyrrolidine-1-yl group that in the 3-position is substituted by an amino-, C_{1-3}-alkylamino- or di-(C_{1-3}-alkyl)amino group,
a piperidine-1-yl- or hexahydroazepine-1-yl group that in the 3-or 4-position is substituted by an amino-, C_{1-3}-alkylamino, or di-(C_{1-3}-alkyl)-amino group,
a C_{5-7}-cycloalkyl group that in the 3-or 4-position is substituted by an amino, C_{1-3}-alkylamino, or di-(C_{1-3}-alkyl)-amino group,
a C_{1-3}-alkylamino group alkylamino group that is substituted at the nitrogen atom by a 2-aminoethyl group, or
a C_{5-7}-cycloalkylamino group that is substituted in the 2-position of the cycloalkyl part by an amino, C_{1-3}-alkylamino, or di-(C_{1-3}-alkyl)-amino group,
the isomers and the salts thereof.

[0010] Especially preferred compounds of the general formula I above are those in which

R^1 means a hydrogen atom, a methyl, ethyl, propyl, 2-propyl, butyl, 2-methylpropyl, 2-propene-1-yl, 2-propyne-1-yl, cyclopropylmethyl, benzyl, 2-phenylethyl, 3-phenylpropyl, 2-hydroxyethyl, 2-methoxyethyl, 2-(dimethylamino)ethyl, or 3-(dimethylamino)propyl group,
R^2 means a methyl group,
R^3 means a 2-butene-1-yl, or 3-methyl-2-butene-1-yl group,
a 1-cyclopentene-1-ylmethyl group,
a 2-butyne-1-yl group,
a benzyl, 2-fluorobenzyl, or 3-fluorobenzyl group, or
a 2-thienylmethyl group, and
R^4 means a 3-aminopyrrolidine-1-yl group,
a 3-aminopiperidine-1-yl, or 4-aminopiperidine-1-yl group,
a 3-aminohexahydroazepin-1-yl, or 4-aminohexahydroazepin-1-yl group,
a 3-aminocyclohexyl group, N-(2-aminoethyl)-methylamino, or
a (2-aminocyclohexyl)amino group,
the isomers thereof and the salts thereof.

[0011] The following preferred compounds may be cited by way of example:

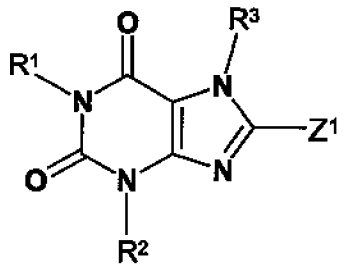
(1) 1,3-dimethyl-7-benzyl-8-(3-aminopyrrolidine-1-yl)-xanthine,
(2) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopyrrolidine-1-yl)-xanthine,
(3) 1,3-dimethyl-7-benzyl-8-(3-aminopiperidine-1-yl)-xanthine,
(4) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-[(trans-2-amino-cyclohexyl)amino]-xanthine,
(5) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine,
(6) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-(4-aminopiperidine-1-yl)-xanthine,
(7) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-[(cis-2-amino-cyclohexyl)amino]-xanthine,
(8) 1,3-dimethyl-7-(2-butyne-1-yl)-8-(3-aminopiperidine-1-y1)-xanthine,
(9) 1,3-dimethyl-7-[(1-cyclopentene-1-yl)methyl]-8-(3-aminopiperidine-1-yl)-xanthine,
(10) 1,3-dimethyl-7-(2-thienylmethyl)-8-(3-aminopiperidine-1-yl)-xanthine,
(11) 1,3-dimethyl-7-(3-fluorobenzyl)-8-(3-aminopiperidine-1-yl)-xanthine,
(12) 1,3-dimethyl-7-(2-fluorobenzyl)-8-(3-aminopiperidine-1-yl)-xanthine,
(13) 1,3-dimethyl-7-(4-fluorobenzyl)-8-(3-aminopiperidine-1-yl)-xanthine,
(14) 1,3-dimethyl-7-(2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine,
(15) 1,3-bis-(cyclopropylmethyl)-7-benzyl-8-(3-aminopiperidine-1-yl)-xanthine,
(16) (R)-1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine,
(17) (S)-1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine,
(18) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminohexahydroazepin-1-yl)-xanthine,

(19) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-(4-aminohexahydroazepin-1-yl)-xanthine,
(20) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-(cis-3-amino-cyclohexyl)-xanthine hydrochloride,
(21) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-(3-methylaminopiperidine-1-yl)-xanthine,
(22) 1-(2-phenylethyl)-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine, and
(23) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-[N-(2-aminoethyl)-methylamino]-xanthine

and the salts thereof.

[0012] In accordance with the invention one obtains the compounds of the general formula I according to processes that are known per se, for example according to the following processes:

a) To prepare compounds of the general formula I, in which R^4 is one of the remainders referred to above that is connected to the xanthine backbone by means of a nitrogen atom:
Reaction of a compound having general formula

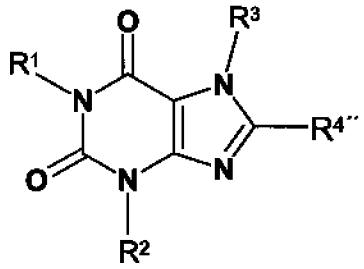


(III),

in which
R^1 to R^3 are defined as referred to above, and
Z^1 represents a leaving group, such as a halogen atom, a substituted hydroxy, mercapto, sulfinyl, sulfonyl, or sulfonyloxy group, such as a chlorine or bromine atom, a methanesulfonyl- or methanesulfonyloxy group having a compound of the general formula

$H\text{-}R^{4'}$, (IV)

in which
$R^{4'}$ represents one of the remainders referred to above for R^4 that is connected to the xanthine backbone of general formula I by means of a nitrogen atom.
The reaction is advantageously performed in a solvent such as isopropanol, butanol, tetrahydrofuran, dioxane, toluene, clorobenzene, dimethyl formamide, dimethyl sulfoxide, methylene chloride, ethylene glycol monomethyl ether, ethylene glycol diethyl ether, or sulfolan, optionally in the presence of an inorganic or tertiary organic base, for example sodium carbonate or calcium hydroxide, a tertiary organic base, for example triethylamine, or in presence of N-ethyldiisopropylamine (Hünig base), where these organic bases may simultaneously serve as solvents, and the reaction may optionally be performed in the presence of a reaction accelerator such as an alkali halogenide or a catalyst based on palladium at temperatures between -20 and 180°C, preferably however at temperatures between -10 and 120°C. The reaction may, however, also be performed without solvent or in an excess amount of the compound of general formula IV.
b) In order to prepare a compound of the general formula I, in which R^4 in accordance with the definition referred to above contains an amino group or an alkylamino group that may optionally be substituted in the alkyl part: Unprotecting a compound of the general formula



(V),

in which R^1, R^2 and R^3 are defined as stated above, and
$R^{4''}$ contains an N-tert.-butyloxycarbonylamino group or an N-tert.-butyloxycarbonyl-N-alkylamino group, where the alkyl part of the N-tert.-butyloxycarbonyl-N-alkylamino group may be substituted as referred to above.

[0013] The cleaving-off of the tert.-butyloxycarbonyl remainder preferably is accomplished by means of treatment with an acid such as trifluoroacetic acid or hydrochloric acid or by treatment with bromotrimethylsilane or iodotrimethylsilane, optionally using a solvent such as methylene chloride, acetate, dioxane, methanol or diethyl ether at temperatures between 0 and 80°C.

[0014] If one obtains a compound the general formula I in accordance with the invention that contains an amino-,

alkylamino, or imino group, this compound may be converted by means of acylation or sulfonylation into a corresponding acyl or sulfonyl compound of general formula I, or

a compound of general formula I that contains an amino, alkylamino, or imino group, this compound may be converted into a corresponding alkyl compound of general formula I by means of alkylation or reductive alkylation, or

a compound of general formula I that contains a carboxy group, this compound may be converted by means of esterification into a corresponding ester of general formula I, or

a compound of general formula I that contains a carboxy or ester group, this compound may be converted by reaction with an amine into a corresponding amide of general formula I.

[0015] The subsequent esterification is optionally performed in a solvent or solvent mixture such as methylene chloride, dimethyl formamide, benzene, toluene, clorobenzene, tetrahydrofuran, benzene/tetrahydrofuran, or dioxane or, in an especially preferred embodiment, in a corresponding alcohol, optionally in the presence of an acid such as hydrochloric acid or in the presence of a dehydrating agent, for example in the presence of chloroformic acid isobutyl ester, thionyl chloride, trimethylchlorosilane, sulfuric acid, methanesulfonic acid, p-toluenesulfonic acid, phosphorus trichloride, phosphorus pentoxide, N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide, or 1-hydroxybenzotriazol and optionally also in the presence of 4-dimethylaminopyridine, N,N'-carbonyldiimidazol, or triphenylphosphine/carbon tetrachloride, advantageously at temperatures between 0 and 150°C, preferably at temperatures between 0 and 80°C.

[0016] The subsequent ester formation may be performed by reacting a compound that contains a carboxy group with a corresponding alkyl halogenide.

[0017] The subsequent acylation or sulfonylation is optionally performed in a solvent or solvent mixture such as methylene chloride, dimethylformamide, benzene, toluene, clorobenzene, tetrahydrofuran, benzene/tetrahydrofuran, or dioxane with a corresponding acyl or sulfonyl derivative, optionally in the presence of a tertiary organic base or in presence of an inorganic base or in presence of a dehydrating agent, for example in the presence of chloroformic acid isobutyl ester, thionyl chloride, trimethylchlorosilane, sulphuric acid, methane sulfonic acid, p-toluenesulfonic acid, phosphorus trichloride, phosphorus pentoxide, N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide, or 1-hydroxybenzotriazol, and optionally also in the presence of 4-dimethylaminopyridine, N,N'-carbonyldiimidazol, or triphenylphosphine/carbon tetrachloride, advantageously at temperatures between 0 and 150°C, preferably at temperatures between 0 and 80°C.

[0018] The subsequent alkylation is optionally performed in a solvent or solvent mixture such as methylene chloride, dimethyl formamide, benzene, toluene, clorobenzene, tetrahydrofuran, benzene/tetrahydrofuran, or dioxane with an alkylating agent such as a corresponding halogenide or sulfonic acid ester, for example, with methyl iodide, ethyl bromide, dimethyl sulfate or benzyl chloride, optionally in the presence of a tertiary organic base or in the presence of an inorganic base, advantageously at temperatures between 0 and 150°C, preferably at temperatures between 0 and 100°C.

[0019] The subsequent reductive alkylation is performed with a corresponding carbonyl compound such as formaldehyde, acetaldehyde, propionaldehyde, acetone or butyraldehyde in the presence of a complex metal hydride such as sodium borohydride, lithium borohydride, sodium triacetoxyborohydride or sodium cyanoborohydride, advantageously at a pH-value of 6-7 and at room temperature or in presence of a hydrogenation catalyst, for example, with hydrogen in the presence of palladium/carbon, at a hydrogen pressure of 1 to 5 bar. The methylation may also be performed in the presence of formic acid as a reducing agent at elevated temperatures, for example, at temperatures between 60 and 120°C.

[0020] The subsequent formation of an amide is accomplished by reacting a corresponding reactive carboxylic acid derivative with a corresponding amine, optionally in a solvent or solvent mixture such as methylene chloride, dimethylformamide, benzene, toluene, clorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxane, where the amine that is used may simultaneously serve as a solvent, optionally in the presence of a tertiary organic base or in presence of an inorganic base or with a corresponding carboxylic acid in the presence of a dehydrating agent, for example, in the presence of chloroformic acid isobutyl ester, thionyl chloride, trimethylchlorosilane, phosphorus trichloride, phosphorus pentoxide, N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide, or 1-hydroxybenzotriazol, and optionally also in the presence of 4-dimethylaminopyridine, N,N'-carbonyldiimidazol, or triphenylphosphine/carbon tetrachloride, advantageously at temperatures between 0 and 150°C, preferably at temperatures between 0 and 80°C.

[0021] In the case of the reactions described above, optionally present reactive groups such as hydroxy, carboxy, amino, alkylamino, or imino groups may be protected during the reaction by customary protective groups that are cleaved off again after the reaction.

[0022] Typical examples of protected groups for a hydroxy group are trimethylsilyl, acetyl, benzoyl, methyl, ethyl, tert.-butyl, trityl, benzyl, or tetrahydropyranyl groups,

protective groups for a carboxy group may be trimethylsilyl, methyl, ethyl, tert.-butyl, benzyl, or tetrahydropyranyl groups,

protective groups for an amino, alkylamino, or imino group may be formyl, acetyl, trifluoracetyl, ethoxycarbonyl, tert.-butoxycarbonyl, benzyloxycarbonyl, benzyl, methoxybenzyl, or 2,4-dimethoxybenzyl groups, and for the amino group also the phthalyl group,

[0023] The cleaving-off of a protected group that may also subsequently occur takes place, for example, hydrolytically in an aqueous solvent, for example, in water, isopropanol/water, acetic acid/water, tetrahydrofuran/water or dioxane/water, in the presence of an acid such as trifluoroacetic acid, hydrochloric acid, or sulphuric acid, or in presence of an alkali base such as sodium hydroxide or calcium hydroxide, or aprotically, for example, in the presence of iodotrimethylsilane, at temperatures between 0 and 120°C, preferably at temperatures between 10 and 100°C.

[0024] The cleaving-off of a benzyl, methoxybenzyl, or benzyloxycarbonyl remainder takes place, however, for example

hydrogenolytically, for example with hydrogen in the presence of a catalyst such as palladium/carbon in a suitable solvent such as methanol, ethanol, acetic acid ethyl ester or glacial acetic acid, optionally with the addition of an acid, such as hydrochloric acid, at temperatures between 0 and 100°C, preferably however at room temperatures between 20 and 60°C, and at a hydrogen pressure of 1 to 7 bar, preferably however of 3 to 5 bar. However, the cleaving-off of a 2,4-dimethoxybenzyl remainder preferably occurs in trifluoroacetic acid in the presence of anisol.

[0025] The cleaving-off of a tert.-butyl- or tert.-butyloxycarbonyl remainder preferably occurs by treating with an acid, such as trifluoroacetic acid or hydrochloric acid, or by treating with iodotrimethylsilane, optionally using a solvent, such as methylene chloride, dioxane, methanol, or diethyl ether.

[0026] The cleaving-off of a trifluoroacetyl remainder preferably occurs by treating with an acid such as hydrochloric acid, optionally in the presence of a solvent, such as acetic acid, at temperatures between 50 and 120°C or by treating with sodium hydroxide solution, optionally in the presence of a solvent, such as tetrahydrofuran, at temperatures between 0 and 50°C.

[0027] The cleaving-off of a phthalyl remainder preferably takes place in the presence of hydrazine or a primary of amine, such as methylamine, ethylamine, or n-butylamine, in a solvent, such as methanol, ethanol, isopropanol, toluene/water, or dioxane, at temperatures between 20 and 50°C.

[0028] Furthermore, the resulting compounds of general formula I may, as already referred to above, be separated into their enantiomers and/or diastereomers. Thus, for example, cis-/trans-mixture may be separated into their cis- and trans- isomers, and compounds having at least one optically active carbon atom may be separated into their enantiomers.

[0029] Thus, for example, the resulting cis-/trans- mixtures may be separated by means of chromatography into their cis- and trans-isomers, the resulting compounds of general formula I that occur in racemates, may be separated by means of methods that are known per se (see Allinger, N. L. and Eliel, E. L. in "Topics in Stereochemistry", Vol. 6, Wiley Interscience, 1971) into their optical antipodes, and compounds of general formula I having at least two asymmetrical carbon atoms based on their physicochemical differences using methods that are known per se, for example, by means of chromatography and/or fractional crystallization, or into their diastereomers, which, if they occur in racemic form, may then be separated into the enantiomers as referred to above.

[0030] The separation of the enantiomers preferably is performed by means of a column separation on chiral phases or by means of recrystallization from an optically active solvent or by means of reaction with an optically active substance that forms salts or derivatives, for example esters or amides, with the racemic compound, for example in particular acids and their activated derivatives or alcohols, and separation of the diastereomeric salt mixture or derivative obtained in this manner, for example on the basis of various solubilities; whereby the free antipodes may be liberated from the pure diastereomeric salts or derivatives through the action of suitable agents. Particularly useful optically active acids are, for example, the D- and L-forms of tartaric acid or dibenzoyltartaric acid, di-o-tolyltartaric acid, malic acid, mandelic acid, camphor sulfonic acid, glutaminic acid, asparaginic acid, or quinic acid. Examples of the optically active alcohol that may be used are (+) or (-) menthol, and examples of the optically active acyl remainder in amides are (+) or (-) menthyloxycarbonyl.

[0031] Moreover, the resulting compounds of formula I may be converted to their salts, in particular for pharmaceutical use into their physiologically compatible salts with inorganic or organic acids. Examples of acids that may be used are hydrochloric acid, hydrobromic acid, sulphuric acid, methanesulfonic acid, phosphoric acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid, or maleic acid.

[0032] In addition, the resulting novel compounds of formula I that are obtained may, if they contain a carboxy group, then be converted if desired into their salts with inorganic or organic bases, in particular for pharmaceutical use into their physiologically compatible salts. Examples of bases that may be used are sodium hydroxide, potassium hydroxide, arginine, cyclohexylamine, ethanolamine, diethanolamine, and triethanolamine.

[0033] The starting compounds of general formulas III and IV are either known in the literature, or they are obtained by means of processes that are known per se in the literature (see Examples I to VIII).

[0034] For example, a starting compound of general formula III is obtained by reacting a theophyllin derivative that is halogenated in the 8-position with a correspondingly substituted alkyl halogenide.

[0035] As already referred to above, the compounds of the invention of general formula I and their physiologically compatible salts exhibit valuable pharmacological properties, in particular an inhibitory effect on the enzyme DPP-IV.

[0036] The biological properties of the novel compounds were tested as follows:

The ability of the substances and their corresponding salts to inhibit the DPP-IV activity may be demonstrated in a test setup in which an extract of the human colon cancer cell line Caco-2 is used as the source of DPP IV. This cell line was obtained from the American Type Culture Collection (ATCC HTB 37). The differentiation of the cells in order to induce the DPP-IV was carried out in accordance with the description provided by Reiher et al. in an article titled "Increased expression of intestinal cell line Caco-2", which appeared in Proc. Natl. Acad. Sci. Vol. 90, pp. 5757-5761 (1993). The cell extract was obtained from cells solubilized in a buffer (10 mM tris HCl, 0.15 M NaCl, 0.04 TIU aprotinin, 0.5% Nonidet-P40, pH 8.0) by centrifugation at 35.000 g for 30 minutes at 4°C (to remove cell debris).

[0037] The DPP-IV assay was performed as follows:

50 µL substrate solution (AFC; AFC is amido-4-trifluoromethylcoumarin), final concentration 100 µM, was first placed in black microtiter plates. 20 µL assay buffer (final concentrations 50 mM tris HCl pH 7.8, 50 mM NaCl, 1% DMSO) was pipetted in. The reaction was initiated by the addition of 30 µL solubilized Caco-2 protein (final concentration 0.14 µg protein per well). The test substances that were to be investigated typically were added in prediluted form in 20 µL, and the assay buffer volume was then reduced accordingly.The reaction was performed at room temperature, and the incubation time was

60 minutes. The fluorescence was then measured in a Victor 1420 Multilabel counter, with the excitation wavelength set at 405 nm and the emission wavelength set at 535 nm. Blank values (corresponding to 0% activity) were obtained in batches without Caco-2 protein (volume replaced by the assay buffer); control values (corresponding to 100% activity) were obtained in batches to which the substance was not added. The effective strengths of the respective test substances, expressed as IC_{50} values, were calculated from dose-effect curves, which each had 11 measuring points. The following results were obtained:

Compound (Example no.)	DPP IV inhibition IC_{50} [nM]
1 (2)	82
1(6)	230
1(15)	624
1(16)	78
1(19)	2770
1(21)	124
1(25)	56
1(27)	125
1(28)	166
1(30)	2050
1(34)	205
1(35)	95
2(1)	22

[0038] The compounds prepared in accordance with the invention exhibit good tolerability, since, for example after the oral administration of 30 mg/kg of the compound of Example 1(2) to rats, no toxic side effects were observed.

[0039] With regard to the ability to inhibit DPP-IV activity, the compounds of the invention of general formula I and their corresponding pharmaceutically acceptable salts are suitable for affecting those conditions or diseases that can be affected by inhibiting DPP-IV activity. It therefore is to be expected that the compounds of the invention are suitable for preventing or treating diseases or conditions such as diabetes mellitus type I and type II, arthritis, adipositas, allograft transplantation, and osteoporosis caused by calcitonin. Additionally, justified by the role of glucagon-like peptides, for example, GLP-1 and GLP-2 and their association with DPP-IV inhibition, it is expected that the compounds of the invention are suitable, among other things, for achieving a sedative or anxiety-lowering effect, and in addition for favorably affecting catabolic conditions following operations or hormonal stress responses, or for reducing mortality and morbidity following myocardial infarctions. Furthermore, they are suitable for treating all conditions that are related to the above effects and are mediated by GLP-1 or GLP-2. The compounds of the invention are also suitable for use as diuretics or antihypertensives and for preventing and treating acute kidney failure. It is also expected that DPP-IV inhibitors, and therefore also the compounds of the invention, can be used to treat infertility or to improve fertility in human beings or in mammals if this infertility is related to insulin resistance, and in particular to polycystic ovarial syndrome.

[0040] The compounds of the invention may also be used in combination with other active ingredients. Therapeutic agents that are suitable for such a combination include, for example, antidiabetics, such as metformin, sulfonyl ureas (for example, glibenclamid, tolbutamid, glimepiride), nateglinide, repaglinide, thiazolidindione (for example, rosiglitazone, pioglitazone), PPAR-gamma-agonists (for example, GI 262570), alpha-glucosidase inhibitors (for example, acarbose, voglibose), insulin and insulin analogues, GLP-1 and GLP-1 analogues (for example, exendin) or amylin, lipid reducers, such as HMG-CoA reductase inhibitors (for example simvastatin, atorvastatin) or fibrate (for example, bezafibrat, fenofibrat) or active ingredients for treating obesity such as sibutramin or tetrahydrolipstatin.

[0041] The dose needed to achieve a corresponding effect with intravenous administration is advantageously 1 to 100 mg, preferably 1 to 30 mg, and with oral administration it is 1 to 1000 mg, preferably 1 to 100 mg, in each case 1 to 4 times daily. To accomplish this, the compounds of formula I prepared in accordance with the invention may be incorporated, possibly in combination with other active ingredients, together with one or more inert conventional carriers and/or diluents, for example, with cornstarch, lactose, sucrose, microcrystalline cellulose, magnesium stearate, polyvinylpyrrolidone, citric acid, tartaric acid, water, water/ethanol, water/glycerin, water/sorbitol, water/polyethylene glycol, propylene glycol, cetylstearyl alcohol, carboxymethylcellulose, or fat-containing substances,

such as hard fat or suitable mixtures thereof in conventional pharmaceutical preparations such as tablets, coated tablets, capsules, powder, suspensions, or suppositories.

[0042] The following examples will be used to illustrate the invention in greater detail:

Preparation of the starting compounds

Example I

1,3-dimethyl-7-benzyl-8-chloroxanthine

[0043] A mixture of 20 g 8-chlorotheophyllin, 150 mL dimethylformamide, 10.2 mL benzyl bromide, and 15.5 mL N-ethyldiisopropylamine is stirred overnight at room temperature. The reaction mixture is poured onto 600 mL water. The solid is vacuum-filtered, washed with water and diethyl ether, and dried.

Yield: 14.6 g (51% of theoretical)

Melting point: 155°C

R_f value: 0.84 (silica gel, glacial acetic acid / methanol = 9 : 1)

[0044] Similar to Example I the following compounds are obtained:

(1) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-chloroxanthine
Melting point: 104°C
Mass spectrum (EI): m/z = 282, 284 $[M]^+$
(2) 1,3-dimethyl-7-(2-butyne-1-yl)-8-chloroxanthine
Melting point: 105-108°C
R_f value: 0.55 (silica gel, methylene chloride / methanol = 20 : 1)
(3) 1,3-dimethyl-7-[(1-cyclopentene-1-yl)methyl]-8-chloroxanthine
R_f value: 0.50 (silica gel, methylene chloride / methanol = 20 : 1)
(4) 1,3-dimethyl-7-(2-thienylmethyl)-8-chloroxanthine
R_f value: 0.35 (silica gel, methylene chloride / methanol = 50 : 1)
Mass spectrum (EI): m/z = 310, 312 $[M]^+$
(5) 1,3-dimethyl-7-(3-fluorobenzyl)-8-chloroxanthine
R_f value: 0.60 (silica gel, methylene chloride / methanol = 20 : 1)
(6) 1,3-dimethyl-7-(2-fluorobenzyl)-8-chloroxanthine
Mass spectrum (EI): m/z = 322, 324 $[M]^+$
(7) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-(cis-3-tert.-butyloxycarbonylaminocyclohexyl)-xanthine
Mass spectrum (ESI^+): m/z = 446 $[M + H]^+$
(8) 1,3-dimethyl-7-(4-fluorobenzyl)-8-chloroxanthine
R_f value: 0.60 (silica gel, methylene chloride / methanol = 20 : 1)
(9) 1,3-dimethyl-7-(2-butene-1-yl)-8-chloroxanthine
R_f value: 0.70 (silica gel, methylene chloride / methanol = 10 : 1)
(10) 3-methyl-7-(3-methyl-2-butene-1-yl)-8-chloroxanthine
Melting point: 226-228°C
R_f value: 0.66 (silica gel, methylene chloride / methanol = 9 : 1)
Mass spectrum (ESI^+): m/z = 269, 271 $[M + H]^+$
(11) 3-methyl-7-(3-methyl-2-butene-1-yl)-8-bromoxanthine
Mass spectrum (ESI^+): m/z = 313, 315 $[M + H]^+$
Rf value: 0.48 (silica gel, methylene chloride / methanol = 10 : 1)
(12) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-[3-(tert.-butyloxycarbonylamino)-propyl]-xanthine
Mass spectrum (ESI^+): m/z = 406 $[M+H]^+$

Example II

(R)-1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-[3-(tert.-butyloxycarbonylamino)-piperidine-1-yl]-xanthine

[0045] A mixture of 1 g 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-chloroxanthine, 1,32 g (R)-3-tert.-butyloxycarbonylaminopiperidine, 1 mL triethylamine, and 10 mL dimethyl formamide is stirred for two and a half days at 50°C. The reaction mixture is diluted with 100 mL water and then extracted with acetate. The organic phase is dried, concentrated, and the residue is stirred together with diethyl ether. The solid is vacuum-filtered and dried.

Yield: 1.0 g (63% of theoretical)

Melting point: 164°C

R_f value: 0.36 (aluminum oxide, cyclohexane/acetate = 1 : 1)

[0046] Similar to Example H, the following compounds are obtained:

(1) (S)-1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-[3-(tert.-butyloxycarbonylamino)-piperidine-1-yl]-xanthine
Melting point: 164°C
Mass spectrum (ESI^-) m/z = 445 $[M - H]^-$
(2) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-[3-(tert.-butyloxycarbonylamino)-hexahydroazepin-1-yl]-xanthine
Melting point: 154°C

Mass spectrum (ESI^-): m/z = 459 [M - H]

(3) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-[4-(tert.-butyloxycarbonylamino)-hexahydroazepin-1-yl]-xanthine

Mass spectrum (ESI^-): m/z = 459 $[M - H]^-$

R_f value: 0.67 (silica gel, acetate)

(4) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-[3-(tert.-butyloxycarbonylamino)-4-methylpiperidine-1-yl]-xanthine

Mass spectrum (ESI^+): m/z = 461 $[M + H]^+$

R_f value: 0.88 (silica gel, glacial acetic acid / methanol = 5 : 1)

Example III

3-(tert.-butyloxycarbonylamino)-hexahydroazepin

[0047] 2 g 1-benzyl-3-(tert.-butyloxycarbonylamino)-hexahydroazepine in 20 mL methanol is hydrogenated for 24 hours at room temperature and a hydrogen pressure of 3 bar in the presence of 200 mg palladium on activated carbon (10% Pd). The catalyst was then removed by means of vacuum-filtration, and the filtrate was concentrated to a dry substance.

Yield: 1.3 g (90% of theoretical)

Melting point: 78°C

Mass spectrum (ESI^+): m/z = 215 $[M + H]^+$

[0048] Similar to Example III, the following compounds are obtained:

(1) (S)-3-(tert.-butyloxycarbonylamino)-piperidine

Melting point: 122°C

Mass spectrum (ESI^+): m/z = 201 $[M + H]^+$

(2) (R)-3-(tert.-butyloxycarbonylamino)-piperidine,

the starting material, (R)-1-benzyl-3-(tert.-butyloxycarbonylamino)-piperidine, was prepared in a manner similar to the (S)-enantiomer disclosed in the literature (Moon, Sung-Hwan; Lee, Sujin; Synth. Commun.; 28; 21; 1998; 3919-3926)

Melting point: 119°C

Mass spectrum (ESI^+): m/z = 201 $[M + H]^+$

(3) 4-(tert.-butyloxycarbonylamino)-hexahydroazepin

Mass spectrum (ESI^+): m/z = 215 $[M + H]^+$

R_f value: 0.02 (aluminum oxide, cyclohexane/acetate = 1 : 1)

(4) 3-(tert.-butyloxycarbonylamino)-4-methylpiperidine

[0049] The crude product is reacted further to obtain the compound of Example II (4).

Example IV

1-benzyl-3-(tert.-butyloxycarbonylamino)-hexahydroazepin

[0050] Prepared by reacting 1-benzyl-3-aminohexahydrobenzazepin with pyrocarboxylic acid-di-tert.-butyl ester

Melting point: 48-50°C

Mass spectrum (ESI^+): m/z = 305 $[M + H]^+$

[0051] Similar to Example IV, the following compounds are obtained:

(1) 1-benzyl-4-(tert.-butyloxycarbonylamino)-hexahydroazepin

Mass spectrum (ESI^+): m/z = 305 $[M + H]^+$

R_f value: 0.79 (aluminum oxide, cyclohexane/acetate = 1 : 1)

(2) 3-(tert.-butyloxycarbonylamino)-4-methylpyridine

Perform using sodium-bis-(trimethylsilyl)-amide/pyrocarboxylic acid-di-tert.-butyl ester in tetrahydrofuran at 0°C.

R_f value: 0.45 (silica gel, acetate)

Example V

1,3-dimethyl-8-(cis-3-tert.-butyloxycarbonylamino-cyclohexyl)-xanthine

prepared from the compound of example VI by treating with 4N sodium hydroxide solution in methanol at 100°C in a bomb tube

Mass spectrum (ESI^+): m/z = 378 $[M + H]^+$

[0052] Similar to Example V the following compound is obtained:

(1) 1,3-dimethyl-8-[3-(tert.-butyloxycarbonylamino)propyl]-xanthine

Mass spectrum (ESI^+): m/z = 338 $[M + H]^+$

Example VI

1,3-dimethyl-5-[(cis-3-tert.butyloxycarbonylamino-cyclohexyl)-carbonylamino]-6-aminouracil

prepared from 5,6-diamino-1,3-dimethyluracil and cis-3-tert.-butyloxycarbonylamino-cyclohexanecarboxylic acid in the presence of O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate and N-ethyl-diisopropylamine in dimethylformamide at room temperature
Mass spectrum (ESI+): m/z = 396 $[M + H]^+$

[0053] Similar to Example VI, the following compound is obtained:

(1) 1,3-dimethyl-5-{[3-(tert.-butyloxycarbonylamino)propyl]carbonylamino}-6-aminouracil

Example VII

1,3-bis-(cyclopropylmethyl)-7-benzyl-8-chloroxanthine

prepared from the compound of the example VIII by reacting with N-chlorosuccinimide in 1,2-dichlorethane under reflux
Mass spectrum (ESI^+): m/z = 407, 409 $[M + Na]^+$

[0054] Similar to Example VII the following compounds are obtained:

(1) 1-methyl-3-(cyclopropylmethyl)-7-benzyl-8-chloroxanthine
Mass spectrum (ESI^+): m/z = 345, 347 $[M + H]^+$
(2) 1,3-diethyl-7-benzyl-8-chloroxanthine
Mass spectrum (ESI^+): m/z = 355, 357 $[M + Na]^+$
(3) 1-methyl-3-ethyl-7-benzyl-8-chloroxanthine
Mass spectrum (ESI^+): m/z = 341, 343 $[M + Na]^+$

Example VIII

1,3-bis-(cyclopropylmethyl)-7-benzylxanthine

prepared from 7-benzylxanthine by reacting with cyclopropylmethyl bromide in dimethylformamide in the presence of cesium carbonate
Mass spectrum (ESI^+): m/z = 351 $[M + H]^+$

[0055] Similar to Example VIII the following compounds are obtained:

(1) 3-(cyclopropylmethyl)-7-benzylxanthine
Mass spectrum (ESI^+): m/z = 297 $[M + H]^+$
(2) 1,3-diethyl-7-benzyl-xanthine
Performed with calcium carbonate
Mass spectrum (ESI^+): m/z = 321 $[M + Na]^+$
(3) 3-ethyl-7-benzylxanthine
Performed with calcium carbonate
Mass spectrum(ESI+): m/z = 293 $[M + Na]^+$

Example IX

1-ethyl-3-methyl-7-(3-methyl-2-butene-1-yl)-8-bromoxanthine

prepared from 3-methyl-7-(3-methyl-2-butene-1-yl)-8-bromoxanthine by reacting with ethyl bromide in the presence of calcium carbonate in dimethylformamide at 70°C
Mass spectrum (ESI^+): m/z = 341, 343 $[M + H]^+$
Retention time: 1.48 min (HPLC, Multosphere 100FBS, 50 mm, 50% acetonitrile)

[0056] Similar to Example IX the following compounds are obtained:

(1) 1-propyl-3-methyl-7-(3-methyl-2-butene-1-yl)-8-bromoxanthine
Mass spectrum (ESI^+): m/z = 355, 357 $[M + H]^+$
(2) 1-butyl-3-methyl-7-(3-methyl-2-butene-1-yl)-8-bromoxanthine
Mass spectrum (ESI^+): m/z = 369, 371 $[M + H]^+$
(3) 1-(2-propyl)-3-methyl-7-(3-methyl-2-butene-1-yl)-8-bromoxanthine
Retention time: 2.11 min (HPLC, Multosphere 100FBS, 50 mm, 50% acetonitrile)
(4) 1-(2-methylpropyl)-3-methyl-7-(3-methyl-2-butene-1-yl)-8-bromoxanthine
Retention time: 2.46 min (HPLC, Multosphere 100FBS, 50 mm, 50% acetonitrile)
(5) 1-(2-propene-1-yl)-3-methyl-7-(3-methyl-2-butene-1-yl)-8-bromoxanthine

Retention time: 1.55 min (HPLC, Multosphere 100FBS, 50 mm, 50% acetonitrile)
Mass spectrum (ESI^+): m/z = 353, 355 $[M + H]^+$
(6) 1-(2-propyne-1-yl)-3-methyl-7-(3-methyl-2-butene-1-yl)-8-bromoxanthine
Retention time: 1.20 min (HPLC, Multosphere 100FBS, 50 mm, 50% acetonitrile)
Mass spectrum (ESI^+): m/z = 351, 353 $[M + H]^+$
(7) 1-(cyclopropylmethyl)-3-methyl-7-(3-methyl-2-butene-1-yl)-8-bromoxanthine
Retention time: 2.19 min (HPLC, Multosphere 100FBS, 50 mm, 50% acetonitrile)
Mass spectrum (ESI^+): m/z = 367, 369 $[M + H]^+$
(8) 1-benzyl-3-methyl-7-(3-methyl-2-butene-1-yl)-8-bromoxanthine
Retention time: 2.40 min (HPLC, Multosphere 100FBS, 50 mm, 50% acetonitrile)
Mass spectrum (ESI^+): m/z = 403, 405 $[M + H]^+$
(9) 1-(2-phenylethyl)-3-methyl-7-(3-methyl-2-butene-1-yl)-8-bromoxanthine
Retention time: 3.29 min (HPLC, Multosphere 100FBS, 50 mm, 50% acetonitrile)
(10) 1-(3-phenylpropyl)-3-methyl-7-(3-methyl-2-butene-1-yl)-8-bromoxanthine
Retention time: 2.95 min (HPLC, Multosphere 100FBS, 50 mm, 50% acetonitrile)
(11) 1-(2-hydroxyethyl)-3-methyl-7-(3-methyl-2-butene-1-yl)-8-bromoxanthine
Retention time: 2.35 min (HPLC, Multosphere 100FBS, 50 mm, 20% acetonitrile)
(12) 1-(2-methoxyethyl)-3-methyl-7-(3-methyl-2-butene-1-yl)-8-bromoxanthine
Retention time: 2.54 min (HPLC, Multosphere 100FBS, 50 mm, 30% acetonitrile)
(13) 1-(3-hydroxypropyl)-3-methyl-7-(3-methyl-2-butene-1-yl)-8-bromoxanthine
Retention time: 2.52 min (HPLC, Multosphere 100FBS, 50 mm, 20% acetonitrile)
(14) 1-[2-(dimethylamino)ethyl]-3-methyl-7-(3-methyl-2-butene-1-yl)-8-bromoxanthine
Retention time: 2.73 min (HPLC, Multosphere 100FBS, 50 mm, 5% acetonitrile)
(15) 1-[3-(dimethylamino)propyl]-3-methyl-7-(3-methyl-2-butene-1-yl)-8-bromoxanthine
Retention time: 2.79 min (HPLC, Multosphere 100FBS, 50 mm, 5% acetonitrile)
(16) 1-methyl-3-(cyclopropylmethyl)-7-benzylxanthine
Perform with methyl iodide at room temperature
Mass spectrum (ESI^+): m/z = 311 $[M + H]^+$
(17) 1-methyl-3-ethyl-7-benzylxanthine
Perform with methyl iodide at room temperature

Example X

1-benzyl-3-(tert.-butyloxycarbonylamino)-4-methylpiperidine

prepared by the catalytic hydrogenation of 1-benzyl-3-(tert.-butyloxycarbonylamino)-4-methylpyridinium bromide in methanol in the presence of platinum dioxide and at a hydrogen pressure of 4 bar.
Mass spectrum (EI): m/z = 304 $[M]^+$

Example XI

1-benzyl-3-(tert.-butyloxycarbonylamino)-4-methylpyridinium bromide

prepared by reacting 3-(tert.-butyloxycarbonylamino)-4-methylpyridine with benzyl bromide in toluene.
Melting point: 200-201°C

Preparation of the final compounds

Example 1

1,3-dimethyl-7-benzyl-8-(3-aminopyrrolidine-1-yl)-xanthine

[0057] A mixture of 200 mg 1,3-dimethyl-7-benzyl-8-chloroxanthine, 420 mg 3-aminopyrrolidine dihydrochloride, 0.92 mL triethylamine, and 2 mL dimethylformamide is stirred for 2 days at 50°C. The reaction mixture is diluted with 20 mL water and extracted two times each with 10 mL acetate. The organic phase is washed with saturated sodium chloride solution, dried, and concentrated. The residue is crystallized with diethyl ether / diisopropyl ether (1 : 1). The solid is vacuum-filtered and dried.
Yield: 92 mg (40% of theoretical)
Melting point: 150°C
Mass spectrum (ESI^+): m/z = 355 $[M + H]^+$
R_f value: 0.08 (silica gel, glacial acetic acid / methanol / conc. aqueous ammonia = 9 : 1 : 0.1) Similar to Example 1, the following compounds are obtained:

(1) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopyrrolidine-1-yl)-xanthine
Melting point: 119°C
Mass spectrum (ESI^+): m/z = 333 $[M + H]^+$
R_f value: 0.07 (silica gel, glacial acetic acid / methanol / conc. aqueous ammonia = 9 : 1 : 0.1)

(2) 1,3-dimethyl-7-benzyl-8-(3-aminopiperidine-1-yl)-xanthine
Mass spectrum (ESI^+): m/z = 369 $[M + H]^+$
R_f value: 0.06 (silica gel, glacial acetic acid / methanol / conc. aqueous ammonia= 9 : 1 : 0.1)
(3) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-[(trans-2-amino-cyclohexyl)amino]-xanthine
Mass spectrum (ESI^+): m/z = 361 $[M + H]^+$
(4) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
Mass spectrum (ESI^+): m/z = 347 $[M + H]^+$
(5) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-(4-aminopiperidine-1-yl)-xanthine
Mass spectrum (ESI^+): m/z = 347 $[M + H]^+$
(6) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-[(cis-2-aminocyclohexy)amino]-xanthine
Mass spectrum (ESI^+): m/z = 361 $[M + H]^+$
(7) 1,3-dimethyl-7-(2-butyne-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
Mass spectrum (ESI^+): m/z = 331 $[M + H]^+$
R_f value: 0.08 (silica gel, glacial acetic acid / methanol / conc. aqueous ammonia = 9 : 1 : 0.1)
(8) 1,3-dimethyl-7-[(1-cyclopentene-1-yl)methyl]-8-(3-aminopiperidine-1-yl)-xanthine
Mass spectrum (ESI^+): m/z = 359 $[M + H]^+$
R_f value: 0.09 (silica gel, glacial acetic acid / methanol / conc. aqueous ammonia = 9 : 1 : 0.1)
(9) 1,3-dimethyl-7-(2-thienylmethyl)-8-(3-aminopiperidine-1-yl)-xanthine
Mass spectrum (ESI^+): m/z = 375 $[M + H]^+$
R_f value: 0.08 (silica gel, glacial acetic acid / methanol / conc. aqueous ammonia = 9 : 1 : 0.1)
(10) 1,3-dimethyl-7-(3-fluorobenzyl)-8-(3-aminopiperidine-1-yl)-xanthine
Mass spectrum (ESI^+): m/z = 387 $[M + H]^+$
R_f value: 0.08 (silica gel, glacial acetic acid / methanol / conc. aqueous ammonia = 9 : 1 : 0.1)
(11) 1,3-dimethyl-7-(2-fluorobenzyl)-8-(3-aminopiperidine-1-yl)-xanthine
Mass spectrum (ESI^+): m/z = 387 $[M + H]^+$
R_f value: 0.08 (silica gel, glacial acetic acid / methanol / conc. aqueous ammonia = 9 : 1 : 0.1)
(12) 1,3-dimethyl-7-(4-fluorobenzyl)-8-(3-aminopiperidine-1-yl)-xanthine
Mass spectrum (ESI^+): m/z = 387 $[M + H]^+$
(13) 1,3-dimethyl-7-(2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
Mass spectrum (ESI^+): m/z = 333 $[M + H]^+$
(14) 1,3-bis-(cyclopropylmethyl)-7-benzyl-8-(3-aminopiperidine-1-yl)-xanthine
Mass spectrum (ESI^+): m/z = 449 $[M + H]^+$
(15) 3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
Mass spectrum (ESI^+): m/z = 333 $[M + H]^+$
(16) 1-ethyl-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
Mass spectrum (ESI^+): m/z = 361 $[M + H]^+$
(17) 1-propyl-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
Mass spectrum ($ES1^+$): m/z = 375 $[M + H]^+$
(18) 1-butyl-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
Mass spectrum (ESI^+): m/z = 389 $[M + H]^+$
(19) 1-(2-propyl)-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
Mass spectrum (ESI^+): m/z = 375 $[M + H]^+$
(20) 1-(2-methylpropyl)-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
Mass spectrum (ESI^+): m/z = 389 $[M + H]^+$
(21) 1-(2-propene-1-yl)-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
Mass spectrum (ESI^+): m/z = 373 $[M + H]^+$
(22) 1-(2-propyne-1-yl)-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
Mass spectrum (ESI^+): m/z = 371 $[M + H]^+$
(23) 1-(cyclopropylmethyl)-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
Mass spectrum (ESI^+): m/z = 387 $[M + H]^+$
(24) 1-benzyl-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
Mass spectrum(ESI+): m/z = 423 $[M + H]^+$
(25) 1-(2-phenylethyl)-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
Mass spectrum (ESI^+): m/z = 437 $[M + H]^+$
(26) 1-(3-phenylpropyl)-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
Mass spectrum (ESI^+): m/z = 451 $[M + H]^+$
(27) 1-(2-hydroxyethyl)-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
Mass spectrum (ESI^+): m/z = 377 $[M + H]^+$
(28) 1-(2-methoxyethyl)-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
Mass spectrum (ESI^+): m/z = 391 $[M + H]^+$
(29) 1-(3-hydroxypropyl)-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
Mass spectrum (ESI^+): m/z = 391 $[M + H]^+$
(30) 1-[2-(dimethylamino)ethyl]-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
Mass spectrum (ESI^+): m/z = 404 $[M + H]^+$
(31) 1-[3-(dimethylamino)propyl]-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
Mass spectrum (ESI^+): m/z = 418 $[M + H]^+$
(32) 1-methyl-3-(cyclopropylmethyl)-7-benzyl-8-(3-aminopiperidine-1-yl)-xanthine
Mass spectrum (ESI^+): m/z = 409 $[M + H]^+$

(33) 1,3-diethyl-7-benzyl-8-(3-aminopiperidine-1-yl)-xanthine
Mass spectrum (ESI^+): m/z = 397 $[M + H]^+$
(34) 1-methyl-3-ethyl-7-benzyl-8-(3-aminopiperidine-1-yl)-xanthine
Mass spectrum (ESI^+): m/z = 383 $[M + H]^+$
(35) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-[N-(2-aminoethyl)-methylamino]-xanthine
Mass spectrum (ESI^+): m/z = 321 $[M + H]^+$

Example 2

(R)-1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperide in-1-yl)-xanthine

[0058] 980 mg (R)-1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-[3-(tert.-butyloxycarbonylamino)-piperidine-1-yl]-xanthine in 12 mL methylene chloride is mixed with 3 mL trifluoroacetic acid and stirred for 2 hours at room temperature. The mixture is then diluted with methylene chloride and adjusted with 1 M sodium hydroxide solution to an alkaline state. The organic phase is separated, dried, and concentrated to produce a dry substance.
Yield: 680 mg (89% of theoretical)
Mass spectrum (ESI^+): m/z = 347 $[M + H]^+$
R_f value: 0.20 (aluminum oxide, glacial acetic acid / methanol = 9 : 1)
[0059] Similar to Example 2 the following compounds are obtained:

(1) (S)-1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
Mass spectrum (ESI^+): m/z = 347 $[M + H]^+$
(2) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminohexahydroazepin-1-yl)-xanthine
Mass spectrum (ESI^+): m/z = 361 $[M + H]^+$
(3) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-(4-aminohexahydroazepin-1-yl)-xanthine
Mass spectrum (ESI^+): m/z = 361 $[M + H]^+$
(4) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-(cis-3-amino-cyclohexyl)-xanthine hydrochloride
The reaction was performed with hydrochloric acid.
^{1}H-NMR (400 MHz, 6 mg in 0.5 mL DMSO-d_6, 30°C): Characteristic signals at 3.03 ppm (1H, m, H-1) and 3.15 ppm (1H, m, H-3)
(5) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopropyl)-xanthine
The reaction was performed with hydrochloric acid.
Mass spectrum (ESI^+): m/z = 306 $[M + H]^+$
(6) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-(3-amino-4-methylpiperidine-1-yl)-xanthine
Mass spectrum (ESI^+): m/z = 361 $[M + H]^+$

Example 3

1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-(3-methylaminopiperidine-1-yl)-xanthine

[0060] 154 mg 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine and 0.032 mL aqueous formaldehyde solution (37 weight percent) in 0.5 mL methanol are mixed with 24 mg sodium boron hydride and stirred at room temperature.
[0061] 0.01 mL formaldehyde solution and 10 mg sodium boron hydride are each added two times, and stirring is continued at room temperature. The reaction mixture is mixed with 1 M sodium hydroxide solution and extracted a number of times with acetate. The organic phases are combined, dried, and concentrated. The residue is purified by means of chromatography over an aluminum oxide column with acetate/methanol.
Yield: 160 mg (25% of theoretical)
Mass spectrum (ESI^+): m/z = 361 $[M + H]^+$
R_f value: 0.80 (aluminum oxide, glacial acetic acid / methanol = 4 : 1)
[0062] Similar to Example 3, the following compound is obtained:

(1) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-(3-dimethylaminopiperidine-1-yl)-xanthine
Mass spectrum (ESI^+): m/z = 375 $[M + H]^+$
R_f value: 0.65 (aluminium oxide, methylene chloride / methanol = 100: 1)

Example 4

(S)-1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-{3-[(2-cyanopyrrolidine-1-ylcarbonylmethyl)amino]-piperidine-1-yl}-xanthine

prepared by reacting the compound of Example 1 (4) with (S)-1-(bromoacetyl)-2-cyano-pyrrolidine in tetrahydrofuran in the presence of triethylamine at room temperature
Melting point: 67-68°C
Mass spectrum (ESI^+): m/z = 505 $[M + Na]^+$

[0063] Similar to the above examples and the other methods disclosed in the literature, the following compounds may also be obtained:

(1) 7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(2) 1-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(3) 3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(4) 1-ethyl-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(5) 1-propyl-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(6) 1-(2-propyl)-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(7) 1-butyl-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(8) 1-(2-butyl)-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(9) 1-(2-methylpropyl)-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(10) 1-(2-propene-1-yl)-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(11) 1-(2-propyne-1-yl)-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(12) 1-cyclopropylmethyl-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(13) 1-benzyl-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(14) 1-(2-phenylethyl)-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(15) 1-(2-hydroxyethyl)-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(16) 1-(2-methoxyethyl)-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(17) 1-(2-ethoxyethyl)-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(18) 1-[2-(dimethylamino)ethyl]-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(19) 1-[2-(diethylamino)ethyl]-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(20) 1-[2-(pyrrolidine-1-yl)ethyl]-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(21) 1-[2-(piperidine-1-yl)ethyl]-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(22) 1-[2-(morpholine-4-yl)ethyl]-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(23) 1-[2-(piperazine-1-yl)ethyl]-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(24) 1-[2-(4-methyl-piperazine-1-yl)ethyl]-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(25) 1-(3-hydroxypropyl)-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(26) 1-(3-methoxypropyl)-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(27) 1-(3-ethoxypropyl)-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(28) 1-[3-(dimethylamino)propyl]-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(29) 1-[3-(diethylamino)propyl]-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(30) 1-[3-(pyrrolidine-1-yl)propyl]-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(31) 1-[3-(piperidine-1-yl)propyl]-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(32) 1-[3-(morpholine-4-yl)propyl]-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(33) 1-[3-(piperazine-1-yl)propyl]-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(34) 1-[3-(4-methyl-piperazine-1-yl)propyl]-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(35) 1-(carboxymethyl)-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(36) 1-(methoxycarbonylmethyl)-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(37) 1-(ethoxycarbonylmethyl)-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(38) 1-(2-carboxyethyl)-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(39) 1-[2-(methoxycarbonyl)ethyl]-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(40) 1-[2-(ethoxycarbonyl)ethyl]-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(41) 1-(aminocarbonylmethyl)-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(42) 1-(methylaminocarbonylmethyl)-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(43) 1-(dimethylaminocarbonylmethyl)-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(44) 1-(pyrrolidine-1-yl-carbonylmethyl)-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(45) 1-(piperidine-1-yl-carbonylmethyl)-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(46) 1-(morpholine-4-yl-carbonylmethyl)-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(47) 1-(cyanomethyl)-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(48) 1-(2-cyanoethyl)-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(49) 1-methyl-3-ethyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(50) 1-methyl-3-propyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(51) 1-methyl-3-(2-propyl)-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(52) 1-methyl-3-butyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(53) 1-methyl-3-(2-butyl)-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(54) 1-methyl-3-(2-methylpropyl)-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(55) 1-methyl-3-(2-propene-1-yl)-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(56) 1-methyl-3-(2-propyne-1-yl)-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(57) 1-methyl-3-cyclopropylmethyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(58) 1-methyl-3-benzyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(59) 1-methyl-3-(2-phenylethyl)-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(60) 1-methyl-3-(2-hydroxyethyl)-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(61) 1-methyl-3-(2-methoxyethyl)-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(62) 1-methyl-3-(2-ethoxyethyl)-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(63) 1-methyl-3-[2-(dimethylamino)ethyl]-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine

(64) 1-methyl-3-[2-(diethylamino)ethyl]-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(65) 1-methyl-3-[2-(pyrrolidine-1-yl)ethyl]-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(66) 1-methyl-3-[2-(piperidine-1-yl)ethyl]-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(67) 1-methyl-3-[2-(morpholin-4-yl)ethyl]-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(68) 1-methyl-3-[2-(piperazine-1-yl)ethyl]-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(69) 1-methyl-3-[2-(4-methyl-piperazine-1-yl)ethyl]-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(70) 1-methyl-3-(3-hydroxypropyl)-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(71) 1-methyl-3-(3-methoxypropyl)-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(72) 1-methyl-3-(3-ethoxypropyl)-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(73) 1-methyl-3-[3-(dimethylamino)propyl]-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(74) 1-methyl-3-[3-(diethylamino)propyl]-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(75) 1-methyl-3-[3-(pyrrolidine-1-yl)propyl]-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(76) 1-methyl-3-[3-(piperidine-1-yl)propyl]-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(77) 1-methyl-3-[3-(morpholin-4-yl)propyl]-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(78) 1-methyl-3-[3-(piperazine-1-yl)propyl]-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(79) 1-methyl-3-[3-(4-methyl-piperazine-1-yl)propyl]-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(80) 1-methyl-3-(carboxymethyl)-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(81) 1-methyl-3-(methoxycarbonylmethyl)-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(82) 1-methyl-3-(ethoxycarbonylmethyl)-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(83) 1-methyl-3-(2-carboxyethyl)-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(84) 1-methyl-3-[2-(methoxycarbonyl)ethyl]-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(85) 1-methyl-3-[2-(ethoxycarbonyl)ethyl]-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(86) 1-methyl-3-(aminocarbonylmethyl)-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(87) 1-methyl-3-(methylaminocarbonylmethyl)-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(88) 1-methyl-3-(dimethylaminocarbonylmethyl)-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(89) 1-methyl-3-(pyrrolidine-1 –yl-carbonylmethyl)-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(90) 1-methyl-3-(piperidine-1 –yl-carbonylmethyl)-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(91) 1-methyl-3-(morpholin-4-yl-carbonylmethyl)-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(92) 1-methyl-3-(cyanomethyl)-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(93) 1-methyl-3-(2-cyanoethyl)-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(94) 1,3,7-trimethyl-8-(3-aminopiperidine-1-yl)-xanthine
(95) 1,3-dimethyl-7-ethyl-8-(3-aminopiperidine-1-yl)-xanthine
(96) 1,3-dimethyl-7-propyl-8-(3-aminopiperidine-1-yl)-xanthine
(97) 1,3-dimethyl-7-(2-propyl)-8-(3-aminopiperidine-1-yl)-xanthine
(98) 1,3-dimethyl-7-butyl-8-(3-aminopiperidine-1-yl)-xanthine
(99) 1,3-dimethyl-7-(2-butyl)-8-(3-aminopiperidine-1-yl)-xanthine
(100) 1,3-dimethyl-7-(2-methylpropyl)-8-(3-aminopiperidine-1-yl)-xanthine
(101) 1,3-dimethyl-7-pentyl-8-(3-aminopiperidine-1-yl)-xanthine
(102) 1,3-dimethyl-7-(2-methylbutyl)-8-(3-aminopiperidine-1-yl)-xanthine
(103) 1,3-dimethyl-7-(3-methylbutyl)-8-(3-aminopiperidine-1-yl)-xanthine
(104) 1,3-dimethyl-7-(2,2-dimethylpropyl)-8-(3-aminopiperidine-1-yl)-xanthine
(105) 1,3-dimethyl-7-cyclopropylmethyl-8-(3-aminopiperidine-1-yl)-xanthine
(106) 1,3-dimethyl-7-[(1-methylcyclopropyl)methyl]-8-(3-aminopiperidine-1-yl)-xanthine
(107) 1,3-dimethyl-7-[(2-methylcyclopropyl)methyl]-8-(3-aminopiperidine-1-yl)-xanthine
(108) 1,3-dimethyl-7-cyclobutylmethyl-8-(3-aminopiperidine-1-yl)-xanthine
(109) 1,3-dimethyl-7-cyclopentylmethyl-8-(3-aminopiperidine-1-yl)-xanthine
(110) 1,3-dimethyl-7-cyclohexylmethyl-8-(3-aminopiperidine-1-yl)-xanthine
(111) 1,3-dimethyl-7-[2-(cyclopropyl)ethyl]-8-(3-aminopiperidine-1-yl)-xanthine
(112) 1,3-dimethyl-7-(2-propene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(113) 1,3-dimethyl-7-(2-methyl-2-propene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(114) 1,3-dimethyl-7-(3-phenyl-2-propene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(115) 1,3-dimethyl-7-(2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(116) 1,3-dimethyl-7-(4,4,4-trifluoro-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(117) 1,3-dimethyl-7-(3-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(118) 1,3-dimethyl-7-(2-chloro-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(119) 1,3-dimethyl-7-(2-brome-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(120) 1,3-dimethyl-7-(3-chloro-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(121) 1,3-dimethyl-7-(3-brom-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(122) 1,3-dimethyl-7-(2-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(123) 1,3-dimethyl-7-(2,3-dimethyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(124) 1,3-dimethyl-7-(3-trifluoromethyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(125) 1,3-dimethyl-7-(3-methyl-3-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(126) 1,3-dimethyl-7-[(2-methyl-1-cyclopentene-1-yl)methyl]-8-(3-aminopiperidine-1-yl)-xanthine
(127) 1,3-dimethyl-7-(1-cyclohexene-1-yl-methyl)-8-(3-aminopiperidine-1-yl)-xanthine
(128) 1,3-dimethyl-7-[2-(1-cyclopentene-1-yl)ethyl]-8-(3-aminopiperidine-1-yl)-xanthine
(129) 1,3-dimethyl-7-(2-propyne-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine

(130) 1,3-dimethyl-7-(3-butyne-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(131) 1,3-dimethyl-7-(4-fluorobenzyl)-8-(3-aminopiperidine-1-yl)-xanthine
(132) 1,3-dimethyl-7-(2-chlorobenzyl)-8-(3-aminopiperidine-1-yl)-xanthine
(133) 1,3-dimethyl-7-(3-chlorobenzyl)-8-(3-aminopiperidine-1-yl)-xanthine
(134) 1,3-dimethyl-7-(4-chlorobenzyl)-8-(3-aminopiperidine-1-yl)-xanthine
(135) 1,3-dimethyl-7-(2-bromobenzyl)-8-(3-aminopiperidine-1-yl)-xanthine
(136) 1,3-dimethyl-7-(3-bromobenzyl)-8-(3-aminopiperidine-1-yl)-xanthine
(137) 1,3-dimethyl-7-(4-bromobenzyl)-8-(3-aminopiperidine-1-yl)-xanthine
(138) 1,3-dimethyl-7-(2-methylbenzyl)-8-(3-aminopiperidine-1-yl)-xanthine
(139) 1,3-dimethyl-7-(3-methylbenzyl)-8-(3-aminopiperidine-1-yl)-xanthine
(140) 1,3-dimethyl-7-(4-methylbenzyl)-8-(3-aminopiperidine-1-yl)-xanthine
(141) 1,3-dimethyl-7-(2-methoxybenzyl)-8-(3-aminopiperidine-1-yl)-xanthine
(142) 1,3-dimethyl-7-(3-methoxybenzyl)-8-(3-aminopiperidine-1-yl)-xanthine
(143) 1,3-dimethyl-7-(4-methoxybenzyl)-8-(3-aminopiperidine-1-yl)-xanthine
(144) 1,3-dimethyl-7-(2-phenylethyl)-8-(3-aminopiperidine-1-yl)-xanthine
(145) 1,3-dimethyl-7-(3-phenylpropyl)-8-(3-aminopiperidine-1-yl)-xanthine
(146) 1,3-dimethyl-7-(2-furanylmethyl)-8-(3-aminopiperidine-1-yl)-xanthine
(147) 1,3-dimethyl-7-(3-furanylmethyl)-8-(3-aminopiperidine-1-yl)-xanthine
(148) 1,3-dimethyl-7-(3-thienylmethyl)-8-(3-aminopiperidine-1-yl)-xanthine
(149) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-(3-methylaminopiperidine-1-yl)-xanthine
(150) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-(3-ethylaminopiperidine-1-yl)-xanthine
(151) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-(3-dimethylaminopiperidine-1-yl)-xanthine
(152) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-(3-diethylaminopiperidine-1-yl)-xanthine
(153) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-{3-[(2-hydroxyethyl)amino]-piperidine-1-yl}-xanthine
(154) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-{3-[N-methyl-N-(2-hydroxyethyl)-amino]-piperidine-1-yl}-xanthine
(155) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-{3-[(3-hydroxypropyl)amino]-piperidine-1-yl}-xanthine
(156) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-{3-[N-methyl-N-(3-hydroxypropyl)-amino]-piperidine-1-yl)-xanthine
(157) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-{3-[(carboxymethyl)amino]piperidine-1-y1}-xanthine
(158) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-{3-[(methoxycarbonylmethy)amino]-piperidine-1-yl}-xanthine
(159) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-{3-[(ethoxycarbonylmethyl)amino]-piperidine-1-yl}-xanthine
(160) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-{3-[N-methyl-N-(methoxycarbonylmethyl)-amino]
piperidine-1-yl}-xanthine
(161) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-{3-[N-methyl-N-(ethoxycarbonylmethyl)-amino]-
piperidine-1-yl}-xanthine
(162) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-{3-[(2-carboxyethyl)amino]piperidine-1-y1}-xanthine
(163) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-(3-{[(2-(methoxycarbonyl)ethyl]-amino}-piperidine-1-yl)-xanthine
(164) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-(3-{(2-(ethoxycarbonyl)ethyl)amino}-piperidine-1-yl)-xanthine
(165) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-(3-{N-methyl-N-(2-(methoxycarbonyl)-ethyl)-amino}-
piperidine-1-yl)-xanthine
(166) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-(3-{N-methyl-N-(2-(ethoxycarbonyl)-ethyl)-amino}-
piperidine-1-yl)-xanthine
(167) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-{3-[(aminocarbonylmethy)amino]-piperidine-1-yl}-xanthine
(168) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-{3-[(methylaminocarbonylmethyl)-amino]piperidine-1-y1}-xanthine
(169) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-{3-[(dimethylaminocarbonylmethyl)-amino]-piperidine-1-yl}-xanthine
(170) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-{3-[(ethylaminocarbonylmethyl)-amino]-piperidine-1-yl}-xanthine
(171) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-{3-[(diethylaminocarbonymethyl)-amino]-piperidine-1-yl}-xanthine
(172) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-{3-[(pyrrolidine-1-ylcarbonylmethyl)-amino]-
piperidine-1-y1}-xanthine
(173) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-{3-[(2-cyanopyrrolidine-1-yl-carbonylmethyl)amino]-
piperidine-1-yl}-xanthine
(174) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-{3-[(4-cyanothiazolidine-3-ylcarbonylmethyl)amino]-piperidine-1-yl}-xanthine
(175) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-{3-[(2-aminocarbonylpyrrolidine-1-ylcarbonylmethy)amino]-piperidine-1-yl}-
xanthine
(176) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-{3-[(2-carboxypyrrolidine-1-ylcarbonylmethyl)amino] -
piperidine-1-yl}-xanthine
(177) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-{3-[(2-methoxycarbonylpyrrolidine-1-ylcarbonylmethyl)amino]piperidine-1-yl}-
xanthine
(178) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-{3-[(piperidine-1-ylcarbonylmethyl)-amino]-piperidine-1-yl}-xanthine
(179) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-{3-[(morpholine-4-ylcarbonylmethyl)-amino]-
piperidine-1-yl}-xanthine

(180) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-(2-methyl-3-aminopiperidine-1-yl)-xanthine
(181) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-(3-methyl-3-aminopiperidine-1-yl)-xanthine
(182) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-(4-methyl-3-aminopiperidine-1-yl)-xanthine
(183) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-(5-methyl-3-aminopiperidine-1-yl)-xanthine
(184) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-(6-methyl-3-aminopiperidine-1-yl)-xanthine
(185) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-(2-amino-8-aza-bicyclo [3.2.1] oct-8-yl)-xanthine
(186) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-(6-amino-2-aza-bicyclo[2.2.2]oct-2-yl)-xanthine
(187) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-(3-amino-cyclopentyl)-xanthine
(188) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-(3-methylamino-cyclohexyl)-xanthine
(189) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-(3-ethylamino-cyclohexyl)-xanthine
(190) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-(3-dimethylamino-cyclohexyl)-xanthine
(191) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-(3-diethylamino-cyclohexyl)-xanthine
(192) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-(4-amino-cyclohexyl)-xanthine
(193) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-[(3-amino-cyclohexyl)aminoxanthine
(194) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-[(2-amino-cyclopentyl)amino]-xanthine
(195) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-[(3-amino-cyclopentyl)amino]-xanthine
(196) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-[(2-amino-cyclobutyl)amino]-xanthine
(197) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-[(3-amino-cyclobutyl)amino]-xanthine
(198) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-[(2-amino-cyclopropyl)amino]-xanthine
(200) 1-[2-(3-fluoro-4-hydroxyphenyl)-ethyl]-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(201) 1-[2-(4-methoxyphenyl)-ethyl]-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(202) 1-[2-(4-ethoxyphenyl)-ethyl]-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(203) 1-(2-{4-[(carboxymethyl)oxy]-phenyl}-ethyl)-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1 yl)-xanthine
(204) 1-(2-{4-[(methoxycarbonyl)methyloxy]-phenyl}-ethyl)-3-methyl-7-(3-methyl-2-butene-1-yl)-
8-(3-aminopiperidine-1-yl)-xanthine
(205) 1-[2-(3-hydroxyphenyl)-ethyl]-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(206) 1-[2-(2-fluoro-5-hydroxyphenyl)-ethyl]-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(207) 1-[2-(3-methoxyphenyl)-ethyl]-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(208) 1-{2-[3-(carboxymethyloxy)-phenyl]-ethyl}-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1yl)-xanthine
(209) 1-(2-{3-[(ethoxycarbonyl)methyloxy]-phenyl}-ethyl)-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-
xanthine
(210) 1-[2-(2-hydroxyphenyl)-ethyl]-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(211) 1-[2-(2-methoxyphenyl)-ethy1]-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(212) 1-{2-[2-(carboxymethyloxy)-phenyl]-ethyl}-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1yl)-xanthine
(213) 1-(2-{2-[(methoxycarbonyl)methyloxy]-phenyl}-ethyl)-3-methyl-7-(3-methyl-2-butene-1-yl)-
8-(3-aminopiperidine-1-yl)-xanthine
(214) 1-[2-(4-methyl-phenyl)-ethyl]-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(215) 1-[2-(4-hydroxymethyl-phenyl)-ethyl]-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(216) 1-[2-(4-carboxyphenyl)-ethyl]-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(217) 1-{2-[4-(methoxycarbonyl)-phenyl]-ethyl}-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(218) 1-{2-[4-(carboxymethyl)-phenyl]-ethyl}-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(219) 1-(2-{4-[(methoxycarbonyl)methyl]-phenyl}-ethyl)-3-methyl-7-(3-methyl-2-butene-1-yl)-8-
(3-aminopiperidine-1-yl)-xanthine
(220) 1-{2-[4-(2-carboxyethyl)-phenyl]-ethyl}-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(221) 1-(2-{4-[2-(methoxycarbonyl)-ethyl]-phenyl}-ethyl)-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-
xanthine
(222) 1-[2-(3-methyl/phenyl)-ethyl]-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(223) 1-[2-(3-carboxyphenyl)-ethyl]-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(224) 1-{2-[3-(ethoxycarbonyl)-phenyl]-ethyl}-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(225) 1-{2-[3-(carboxymethyl)-phenyl]-ethyl}-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(226) 1-(2-{3-[(methoxycarbonyl)methyl]-phenyl}-ethyl)-3-methyl-7-(3-methyl-2-butene-1-yl)-8-
(3-aminopiperidine-1-yl)-xanthine
(227) 1-{2-[3-(2-carboxyethyl)-phenyl]-ethyl}-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(228) 1-(2-{3-[2-(methoxycarbonyl)-ethyl]-phenyl}-ethyl)-3-methyl-7-(3-methyl-2-butene-1-yl)-
8-(3-aminopiperidine-1-yl)-xanthine

(229) 1-[2-(2-methyl-phenyl)-ethyl]-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(230) 1-[2-(2-carboxyphenyl)-ethyl]-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(231) 1-(2-[2-(methoxycarbonyl)-phenyl]-ethyl)-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(232) 1-[2-(4-fluorophenyl)-ethyl]-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(233) 1-[2-(4-chlorophenyl)-ethyl]-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(234) 1-[2-(4-bromophenyl)-ethyl]-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(235) 1-[2-(4-cyanophenyl)-ethyl]-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(236) 1-[2-(4-trifluoromethoxyphenyl)-ethyl]-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(237) 1-[2-(4-methylsulfanylphenyl)-ethyl]-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(238) 1-[2-(4-methylsulfinylphenyl)-ethyl]-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(239) 1-[2-(4-methylsulfonylphenyl)-ethyl]-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(240) 1-[2-(4-trifluoromethyl-phenyl)-ethyl]-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(241) 1-[2-(4-aminophenyl)-ethyl]-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(242) 1-(2-{4-[(methylcarbonyl)amino]-phenyl}-ethyl)-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(243) 1-(2-{4-[(methylsulfonyl)aminophenyl}-ethyl)-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(244) 1-[2-(3-nitro-phenyl)-ethyl]-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(245) 1-{2-[4-(aminocarbonyl)-phenyl]-ethyl}-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(246) 1-{2-[4-(methylaminocarbonyl)-phenyl]-ethyl}-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(247) 1-{2-[4-(dimethylaminocarbonyl)-phenyl]-ethyl}-3-methyl-7-(3-methyl-2-butene-1-yl)-
8-(3-aminopiperidine-1-yl)-xanthine
(248) 1-{2-[4-(aminosulfonyl)-phenyl]-ethyl}-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(249) 1-{2-[4-(methylaminosulfonyl)-phenyl]-ethyl}-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(250) 1-{2-[4-(dimethylaminosulfonyl)-phenyl]-ethyl}-3-methyl-7-(3-methyl-2-butene-1-yl)-
8-(3-aminopiperidine-1-yl)-xanthine
(251) 1-(3-carboxypropyl)-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(252) 1-[3-(methoxycarbonyl)-propyl]-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(253) 1-[3-(ethoxycarbonyl)-propyl]-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(254) 1-[2-(3,4-dimethyl-phenyl)-ethyl]-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(255) 1-[2-(2-fluoro-5-chlorophenyl)-ethyl]-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(256) 1-[2-(3,5-dimethoxyphenyl)-ethyl]-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(257) 1-[2-(naphthalene-2-yl)-ethyl]-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(258) 1-[2-(pyridine-3-yl)-ethyl]-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(259) 1-[4-phenylbutyl]-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(260) 1-methyl-3-(3-phenylpropyl)-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(261) 1-methyl-3-(3-carboxypropyl)-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(262) 1-methyl-3-[3-(methoxycarbonyl)-propyl]-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(263) 1-methyl-3-[3-(ethoxycarbonyl)-propyl]-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine
(264) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-(3-amino-1-methylprop-1-yl)-xanthine
(265) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-(3-amino-1,1-dimethyl-prop-1-yl)-xanthine
(266) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-(3-amino-1-methyl-but-1-yl)-xanthine
(267) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-[1-(2-amino-ethyl)-cyclopropyl]-xanthine
(268) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-[1-(aminomethyl)-cyclopentylmethyl]-xanthine
(269) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-[2-(aminomethyl)-cyclopropyl]-xanthine
(270) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-[2-(aminomethyl)-cyclopentyl]-xanthine
(271) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-(2-amino-eyelopropylmethyl)-xanthine
(272) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-[(piperidine-3-yl)methyl]-xanthine
(273) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-[2-(pyrrolidine-2-yl)-ethyl]-xanthine
(274) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-[N-(2-amino-ethyl)-N-ethyl-amino]-xanthine
(275) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-[N-(2-amino-ethyl)-N-isopropylamino]-xanthine
(276) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-[N-(2-amino-ethyl)-N-cyclopropyl amino] -xanthine
(277) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-[N-(2-amino-ethyl)-N-cyclopropylmethylamino]-xanthine
(278) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-[N-(2-amino-ethyl)-N-phenylamino]-xanthine
(279) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-[N-(2-amino-ethyl)-N-benzylamino]-xanthine
(280) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-[N-(2-amino-1-methyl-ethyl)-N-methylamino]-xanthine

(281) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-[N-(2-aminoprop-1-yl)-N-methylamino]-xanthine
(282) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-[N-(2-amino-1-methyl-prop-1-yl)-N-methylamino]-xanthine
(283) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-[N-(2-amino-2-methylpropyl)-N-methylamino]-xanthine
(284) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-[N-(1-aminocyclopropylmethyl)-N-methylamino]-xanthine
(285) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-[N-(2-amino-cyclopropyl)-N-methylamino]-xanthine
(286) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-[N-(2-amino-cyclobutyl)-N-methylamino]-xanthine
(287) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-[N-(2-amino-cyclopentyl)-N-methylamino]-xanthine
(288) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-[N-(2-aminocyclohexyl)-N-methylamino]-xanthine
(289) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-[N-(pyrrolidine-2-yl)methyl]-N-methylamino]-xanthine
(290) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-[N-(pyrrolidine-3-yl)-N-methylamino]-xanthine
(291) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-[N-(piperidine-3-yl)-N-methylamino]-xanthine

Example 4

Coated tablets containing 75 mg active ingredient

1 coated table core contains:	
Active ingredient	75.0 mg
Calcium phosphate	93.0 mg
Cornstarch	35.5 mg
Polyvinylpyrrolidone	10.0 mg
Hydroxypropylmethylcellulose	15.0 mg
Magnesium stearate	1.5 mg
	230.0 mg

Preparation

[0064] The active substance is mixed with calcium phosphate, cornstarch, polyvinylpyrrolidone, hydroxypropylmethylcellulose, and half of the indicated quantity of magnesium stearate. Tablets having a diameter of approximately 13 mm are prepared on a tabletting machine; these tablets are rubbed through a screen having a 1.5 mm screen opening and mixed with the remaining amount of magnesium stearate. This granulate is compressed into tablets having the desired shape on the tabletting machine.
Core weight: 230 mg
Die: 9 mm, curved
[0065] The coated-tablet cores prepared in this manner are coated with a film that mainly consists of hydroxypropylmethylcellulose. The finished coated tablets are polished with beeswax.
Coated tablet weight: 245 mg

Example 5

Tablets containing 100 mg active ingredient

Composition

1 tablet contains:

Active ingredient	100.0 mg
Lactose	0.0 mg
Cornstarch	4.0 mg
Polyvinylpyrrolidone	4.0 mg
Magnesium stearate	2.0 mg
	220.0 mg

Preparation method

[0066] The active ingredient, lactose, and starch are mixed and uniformly moistened with an aqueous solution of polyvinylpyrrolidone. After the moist mass has been screened (2.0 mm mesh opening) and dried in a tray dryer at 50°C, the screening is repeated (1.5 mm mesh opening), and the lubricant is mixed in. A ready-to-compress mixture is processed into tablets.
Tablet weight: 220 mg
Diameter: 10 mm, biplanar with facet on both sides and a score line on one side.

Example 6

Tablets containing 150 mg active ingredient

Composition

1 tablet contains:

Active ingredient	150.0 mg
Lactose powder	89.0 mg
Cornstarch	40.0 mg
Colloidal silica gel acid	10.0 mg
Polyvinylpyrrolidone	10.0 mg
Magnesium stearate	1.0 mg
	300.0 mg

Preparation

[0067] The active ingredient mixed with lactose, cornstarch, and silicic acid is moistened with a 20% aqueous polyvinylpyrrolidone solution and forced through a screen having a 1.5 mm mesh opening.

[0068] The granulate, which is dried at 45°C, once again is rubbed through the same screen and mixed with the stated quantity of magnesium stearate. Tablets are pressed out of the mixture.

Tablet weight: 300 mg

Die: 10 mm, flat

Example 7

Hard gelatin capsules with 150 mg active ingredient

1 capsule contains:

Active ingredient	150.0 mg
Cornstarch, dried	approx. 180.0 mg
Lactose powder.	approx. 87.0 mg
Magnesium stearate	3.0 mg
approx.	420.0 mg

Preparation

[0069] The active ingredient is mixed with the excipients, forced through a screen having a 0.75 mm mesh opening, and mixed in a suitable apparatus until a homogeneous condition is achieved. The final mixture is filled into size-1 hard gelatin capsules.

Capsule contents: approx. 320 mg

Capsule shell: Hard gelatin capsule size 1.

Example 8

Suppositories containing 150 mg active ingredient

1 suppository contains:

Active ingredient	150.0 mg
Polyethylene glycol 1500	550.0 mg
Polyethylene glycol 6000	460.0 mg
Polyoxyethylene sorbitan monostearate	840.0 mg
	2000.0 mg

Preparation

[0070] After the suppository material has been melted, the active ingredient is homogeneously incorporated into the melt, and the melt is poured into precooled molds.

Example 9

Suspension containing 50 mg active ingredient

[0071] 100 mL suspension contains:

Active ingredient	1.00 g
Carboxymethylcellulose Na salt	0.10 g
p-hydroxybenzoic acid methyl ester	0.05 g
p-hydroxybenzoic acid propyl ester	0.01 g
Sucrose	10.00 g
Glycerin	5.00 g
Sorbitol solution 70%	20.00 g
Fragrance	0.30 g
Water, dist.	to make 100 mL

Preparation

[0072] Distilled water is heated to 70°C. In it, while stirring, p-hydroxybenzoic acid methyl ester and propyl ester as well as glycerin and carboxymethylcellulose sodium salt are dissolved. The mixture is cooled to room temperature, and while stirring the active ingredient is added and dispersed to a homogeneous condition. After the sugar, the sorbitol solution, and the fragrance have been added and dissolved, the suspension is evacuated while stirring to remove any air that may be present.
5 mL suspension contains 50 mg active ingredient.

Example 10

Ampoules containing 10 mg active ingredient

Composition

Active ingredient	10.0 mg
0.01 n hydrochloric acid with suff. quant. double-dist. water to make	2.0 mL

Preparation

[0073] The active substance is dissolved in the required quantity of 0.01 n HCl, adjusted to an isotonic condition with sodium chloride, sterile-filtered, and filled into 2 mL ampoules.

Example 11

Ampoules containing 50 mg active ingredient

Composition

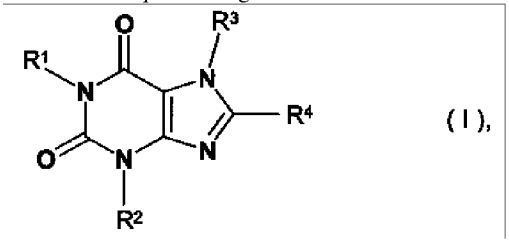
Active ingredient	50.0 mg
0.01 n hydrochloric acid with suff. quant. double-distilled water to make	10.0 mL

Preparation

[0074] The active substance is dissolved in the required quantity of 0.01 n HCl, adjusted to an isotonic condition with sodium chloride, sterile-filtered, and filled into 10 mL ampoules.

Patent claims

1. Compounds of general formula



(I),

in which
R^1 means a hydrogen atom,
a C_{1-6}-alkyl group,
a C_{1-6}-alkyl group substituted by an R_a group, where
R_a means a C_{3-7}-cycloalkyl, heteroaryl, cyano, carboxy, C_{1-3}-alkoxy-carbonyl, aminocarbonyl, C_{1-3}-alkylamino-carbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl, pyrrolidine-1-ylcarbonyl, piperidine-1-ylcarbonyl, morpholine-4-ylcarbonyl, piperazine-1-ylcarbonyl, 4-methylpiperazine-1-ylcarbonyl, or 4-ethylpiperazine-1-ylcarbonyl group,
a C_{1-6}-alkyl group substituted by a phenyl group, where the phenyl ring is substituted by the groups R^{10} to R^{14} and
R^{10} means a hydrogen atom,
a fluorine, chlorine, bromine, or iodine atom,
a C_{1-3}-alkyl, hydroxy, or C_{1-3}-alkoxy group,
a nitro, amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)amino, pyrrolidine-1-yl, piperidine-1-yl, morpholine-4-yl, piperazine-1-yl, 4-(C_{1-3}-alkyl)-piperazine-1-yl, C_{1-3}-alkylcarbonylamino, arylcarbonylamino, aryl-C_{1-3}-alkylcarbonylamino, C_{1-3}-alkyloxycarbonylamino, C_{1-3}-alkylsulfonylamino, arylsulfonylamino, or aryl-C_{1-3}-alkyl-sulfonylamino group,
an N-(C_{1-3}-alkyl)-C_{1-3}-alkylcarbonylamino, N-(C_{1-3}-alkyl)-arylcarbonylamino, N-(C_{1-3}-alkyl)-aryl-C_{1-3}-alyl-carbonylamino, N-(C_{1-3}-alkyl)-C_{1-3}-alkyloxycarbonylamino, N-(C_{1-3}-alkyl)- C_{1-3}-alkylsulfonylamino, N-(C_{1-3}-alkyl)-arylsulfonylamino, or N-(C_{1-3}-alkyl)-aryl-C_{1-3}-alkyl-sulfonylamino group,
a cyano, carboxy, C_{1-3}-alkyloxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl, pyrrolidine-1-yl-carbonyl, piperidine-1-yl-carbonyl, morpholine-4-yl-carbonyl, piperazine-1-ylcarbonyl, or 4-(C_{1-3}-alkyl)-piperazine- 1 -yl-carbonyl group,
a C_{1-3}-alkyl-carbonyl or an arylcarbonyl group,
eine carboxy-C_{1-3}-alkyl, C_{1-3}-alkyloxycarbonyl-C_{1-3}-alkyl, cyano-C_{1-3}-alkyl, aminocarbonyl- C_{1-3}-alkyl, C_{1-3}-alkyl-aminocarbonyl-C_{1-3}-alkyl, di-(C_{1-3}-alkyl)-aminocarbonyl-C_{1-3}alkyl, pyrrolidine-1-yl-carbonyl-C_{1-3}- alkyl, piperidine-1-yl-carbonyl-C_{1-3}-alkyl, morpholine-4-yl-carbonyl- C_{1-3}-alkyl, piperazine-1-yl-carbonyl-C_{1-3}-alkyl, or 4-(C_{1-3}-alkyl)-piperazine-1-yl-carbonyl-C_{1-3}-alkyl group,
a carboxy-C_{1-3}-alkyloxy, C_{1-3}-alkyloxycarbonyl-C_{1-3}-alkyloxy, cyano-C_{1-3}-alkyloxy, aminocarbonyl-C_{1-3}-alkyloxy, C_{1-3}-alkylaminocarbonyl-C_{1-3}-alkyloxy, di-(C_{1-3}-alkyl)-aminocarbonyl-C_{1-3}-alkyloxy, pyrrolidine-1-yl-carbonyl-C_{1-3}-alkyloxy, piperidine-1-yl-carbonyl- C_{1-3}-alkyloxy, morpholine-4-yl-carbonyl-C_{1-3}-alkyloxy, piperazine- 1-yl-carbonyl-C_{1-3}-alkyloxy, or 4-(C_{1-3}-alkyl)-piperazine-1-yl-carbonyl-C_{1-3}-alkyloxy group,
a hydroxy- C_{1-3}-alkyl, C_{1-3}-alkoxy-C_{1-3}-alkyl, amino-C_{1-3}-alkyl, C_{1-3}-alkylamino-C_{1-3}-alkyl, di-(C_{1-3}-alkyl)-amino-C_{1-3}-pyrrolidine-1-yl-C_{1-3}-alkyl, piperidine-1-yl-C_{1-3}-alkyl, morpholine-4-yl- C_{1-3}-alkyl, piperazine-1-yl-C_{1-3}-alkyl, 4-(C_{1-3}-alkyl)-piperazine-1-yl-C_{1-3}-alkyl group,
a hydroxy-C_{1-3}-alkyloxy, C_{1-3}-alkoxy-C_{1-3}-alkyloxy, amino-C_{1-3}-alkyloxy, amino-C_{1-3}-alkyloxy, C_{1-3}-alkylamino-C_{1-3}-alkyloxy, di (C_{1-3}-alkyl)-amino-C_{1-3}-alkyloxy, pyrrolidine-1-yl- C_{1-3}-alkyloxy, piperidine-1-yl- C_{1-3}-alkyloxy, morpholine-4-yl- C_{1-3}-alkyloxy, piperazine-1-yl- C_{1-3}-alkyloxy, 4-(C_{1-3}-alkyl)-piperazine-1-yl-C_{1-3}-alkyloxy group,
a mercapto, C_{1-3}-alkylsulfenyl, C_{1-3}-alkysulfinyl, C_{1-3}-alkylsulfonyl, C_{1-3}-alkylsulfonyloxy, trifluormethylsulfenyl, trifluormethylsulfinyl, or trifluormethylsulfonyl group,
a sulfo, aminosulfonyl, C_{1-3}-alkylaminosulfonyl, di-(C_{1-3}-alkyl)-aminosulfonyl, pyrrolidine-1-yl-sulfonyl, piperidine-1-yl-sulfonyl, morpholine-4-yl-sulfonyl, piperazine-1-yl-sulfonyl, or 4-(C_{1-3}-alkyl)-piperazine-1-yl-sulfonyl group,
a methyl or methoxy group substituted by 1 to 3 fluorine atoms,
an ethyl or ethoxy group substituted by 1 to 5 fluorine atoms,
a C_{2-4}-alkenyl or C_{2-4}-alkinyl group,
a 2-propene-1-yloxy or 2-propyne-1-yloxy group,
a C_{3-6}-cycloalkyl or C_{3-6}-cycloalkoxy group,
a C_{3-6}-cycloalkyl-C_{1-3}-alkyl, or C_{3-6}-cycloalkyl-C_{1-3}-alkoxy group or
an aryl, aryloxy, aryl-C_{1-3}-alkyl, or aryl-C_{1-3}-alkoxy group,
R^{11} and R^{12}, which may be identical or different, each mean a hydrogen atom, a fluorine, chlorine, bromine, or iodine atom, a C_{1-3}-alkyltrifluoromethyl, hydroxy, or C_{1-3}-alkoxy group or a cyano group, or
R^{11} together with R^{12}, if these remainders are bonded to adjacent carbon atoms, also mean a methylenedioxy, linear C_{3-5}-alkylene, -CH=CH-CH=CH-, -CH=CH-CH=N-, or -CH=CH-N=CH- group, and
R^{13} and R^{14}, which may be identical or different, each mean a hydrogen atom, a fluorine, chlorine, or bromine atom, a trifluoromethyl, C_{1-3}-alkyl or C_{1-3}-alkoxy group,
a C_{2-6}-alkyl group substituted by an R_b group, where
R_b is isolated from the ring nitrogen atom by at least two carbon atoms, and
R_b means a hydroxy, C_{1-3}-alkoxy, amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino, pyrrolidine-1-yl, piperidine-1-yl, morpholine-4-yl, piperazine-1-yl, 4-methylpiperazine-1-yl, or 4-ethylpiperazine-1-yl group,
a C_{3-6}-cycloalkyl group, or
a C_{3-4}-alkenyl or C_{3-4}-alkinyl group, where the multiple bond is isolated from the ring nitrogen atom by at least one carbon atom,
R^2 means a hydrogen atom,
a C_{1-6}-alkyl group,
a C_{1-6}-alkyl group substituted by a phenyl group, where the phenyl ring is substituted by the groups R^{10} to R^{14}, and $R^{10}$to R^{14} are defined as stated above,
a C_{1-6}-alkyl group substituted by an R_a group, where

R_a means a C_{3-7}-cycloalkyl, heteroaryl, cyano, carboxy, C_{1-3}-alkoxy-carbonyl, aminocarbonyl, C_{1-3}-alkyl-aminocarbonyl, or di-(C_{1-3}-alkyl)-aminocarbonyl, pyrrolidine-1-ylcarbonyl, piperidine-1-ylcarbonyl, morpholine-4-ylcarbonyl, piperazine-1-ylcarbonyl, 4-methylpiperazine-1-ylcarbonyl, or 4-ethylpiperazine-1-ylcarbonyl group,
a C_{2-6}-alkyl group substituted by an R_b group, where
R_b is isolated from the ring nitrogen atom by at least two carbon atoms, and
R_b means a hydroxy, C_{1-3}-alkoxy, amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino, pyrrolidine-1-yl, piperidine-1-yl, morpholine-4-yl, piperazine-1-yl, 4-methylpiperazine-1-yl, or 4-ethylpiperazine-1-yl group, a C_{3-6}-cycloalkyl group, or
a C_{3-4}-alkenyl or C_{3-4}-alkinyl group, where the multiple bond is isolated from the ring nitrogen atom by at least one carbon atom,
R^3 means a C_{1-6}-alkyl group,
a C_{1-6}-alkyl group substituted by an R_c group, where
R_c means a C_{3-7}-cycloalkyl group optionally substituted by a C_{1-3}-alkyl group,
a C_{5-7}-cycloalkenyl group optionally substituted by a C_{1-3}-alkyl group, or
means an aryl or heteroaryl group,
a linear or branched C_{3-8}-alkenyl group, in which the double bond is isolated from the ring nitrogen atom by at least one carbon atom,
a linear or branched C_{3-6}-alkenyl group that is substituted by a chlorine or bromine atom, an aryl or trifluoromethyl group, and in which the double bond is isolated from the ring nitrogen atom by at least one carbon atom,
or a linear or branched C_{3-6}-alkinyl group, in which the triple bond is isolated from the ring nitrogen atom by at least one carbon atom, and
R^4 means an azetidine-1-yl or pyrrolidine-1-yl group, which in the 3-position is substituted by an R_eNR_d group and which also may be substituted by one or two C_{1-3}-alkyl groups, where
R_e means a hydrogen atom or a C_{1-3}-alkyl group, and
R_d means a hydrogen atom, a C_{1-3}-alkyl group, an R_f- C_{1-3}-alkyl group, or an R_g-C_{2-3}-alkyl group, where
R_f means a carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl, pyrrolidine-1-yl-carbonyl, 2-cyanopyrrolidine-1-yl-carbonyl, 2-carboxypyrrolidine- 1-yl-carbonyl, 2-methoxycarbonylpyrrolidine- 1-yl-carbonyl, 2-ethoxycarbonylpyrrolidine-1-yl-carbonyl, 2-aminocarbonylpyrrolidine-1-yl-carbonyl, 4-carboxythiazolidine-3-yl-carbonyl, 4-carboxythiazolidin-3-yl-carbonyl, 4-methoxycarbonylthiazolidine-3-yl-carbonyl, 4-ethoxycarbonylthiazolidine-3-yl-carbonyl, 4-aminocarbonylthiazolidine-3-yl-carbonyl, piperidine- 1-yl-carbonyl, morpholine-4-yl-carbonyl, piperazine-1-yl-carbonyl, 4-methyl-piperazine-1-yl-carbonyl, or 4-ethyl-piperazine-1-yl-carbonyl group, and
R_g, which is separated by at least two carbon atoms from the nitrogen atom of the R_eNR_d group, means a hydroxy, methoxy, or ethoxy group,
a piperidine-1-yl or hexahydroazepine-1-yl group, which in the 3-position or in the 4-position is substituted by an R_eNR_d group and which also may be substituted by one or two C_{1-3}-alkyl groups, where R_e and R_d are defined as stated above,
a piperidine-1-yl or hexahydroazepine-1-yl group, that is substituted in the 3-position by an amino, C_{1-3}-alkylamino, or di-(C_{1-3}-alkyl)-amino group and in which in each case two hydrogen atoms are substituted on the carbon backbone of the piperidine-1-yl or hexahydroazepine-1-yl group by a linear alkylene bridge, where said bridge contains 2 to 5 carbon atoms if the two hydrogen atoms are located at the same carbon atom, or 1 to 4 carbon atoms if the hydrogen atoms are located on adjacent carbon atoms, or 1 to 4 carbon atoms if the hydrogen atoms are located on carbon atoms that are separated by one atom, or 1 to 3 carbon atoms if the two hydrogen atoms are located at carbon atoms that are separated by two atoms,
a C_{3-7}-cycloalkyl group substituted by an amino, C_{1-3}-alkylamino, or di-(C_{1-3}-alkyl)-amino group, a C_{3-7}-cycloalkylamino, or N-(C_{1-3}-alkyl)-C_{3-7}-cycloalkylamino group substituted in the cycloalkyl part by an amino, C_{1-3}-alkylamino, or di-(C_{1-3}-alkyl)-amino group, where the two nitrogen atoms on the cycloalkyl part are separated from each other by at least two carbon atoms,
an amino group substituted by the remainders R^{15} and R^{16}, in which
R^{15} means a C_{1-6}-alkyl group, a C_{3-6}-cycloalkyl, C_{3-6}-cycloalkyl-C_{1-3}-alkyl, aryl, or aryl-C_{1-3}-alkyl group, and
R^{16} represents an R^{17}-C_{2-3}-alkyl group, where the C_{2-3}-alkyl part is linear and may be substituted by one to four C_{1-3}-alkyl groups, which may be identical or different, and
R^{17} means an amino, C_{1-3}-alkylamino, or di-(C_{1-3}-alkyl)-amino group, where, if R^3 means a methyl group, R^{17} must not represent a di-(C_{1-3}-alkyl)-amino group,
an amino group substituted by the remainders R^{15} and R^{18}, in which
R^{15} is defined as stated above, and R^{18} represents a C_{3-6}-cycloalkyl-methyl group that is substituted in the 1-position of the cycloalkyl remainder by R^{19} or a C_{3-6}-cycloalkyl group substituted in the 1-position by an R^{19}-CH_2- group, where R^{19} represents an amino, C_{1-3}-alkylamino, or di-(C_{1-3}-alkyl)-amino group,
an amino group substituted by the remainders R^{15} and R^{20}, in which
R^{15} is defined as stated above and R^{20} represents an azetidine-3-yl, azetidine-2-ylmethyl, azetidine-3-ylmethyl, pyrrolidine-3-yl, pyrrolidine-2-ylmethyl, pyrrolidine-3-ylmethyl, piperidine-3-yl, piperidine-4-yl, piperidine 2-ylmethyl, piperidine-3-ylmethyl, or piperidine-4-ylmethyl group, where the remainders referred to for R^{20} may be substituted in each case by one or two C_{1-3}-alkyl groups,

an R^{17}-C_{3-4}-alkyl group, in which the C_{3-4}-alkyl part is linear and is substituted by the remainder R^{15} and may additionally be substituted by one or two C_{1-3}-alkyl groups, where R^{15} and R^{17} are defined as stated above,
a C_{3-6}-cycloalkyl-CH_2CH_2- group substituted in the 1-position of the cycloalkyl remainder by R^{19}, a C_{3-6}-cycloalkyl-CH_2- group substituted in the 1-position of the cycloalkyl remainder by an R^{19}-CH_2 group, or a C_{3-6}-cycloalkyl group substituted in the 1-position by an R^{19}-CH_2CH_2 group, where R^{19} is defined as stated above,
a C_{3-6}-cycloalkylmethyl group substituted in the 2-position of the cycloalkyl residue by R^{19} or a C_{3-6}-cycloalkyl group substituted in the 2-position by an R^{19}-CH_2 group, where R^{19} is defined as stated above,
or an azetidine-2-yl-C_{1-2}-alkyl, azetidine-3-yl-C_{1-2}-alkyl, pyrrolidine-2-yl-C_{1-2}-alkyl, pyrrolidine-3-yl, pyrrolidine-3-yl-C_{1-2}-alkyl, piperidine-2-yl-C_{1-2}-alkyl, piperidine-3-yl, piperidine-3-yl-C_{1-2}-alkyl, piperidine-4-yl, or piperidine-4-yl-C_{1-2}-alkyl group, where the groups referred to above may each be substituted by one or two C_{1-3}-alkyl groups,
where the aryl groups referred to in the definition of the above remainders are phenyl groups that may be monosubstituted or disubstituted independently of each other by R_h, where the substituents may be identical or different, and R_h represents a fluorine, chlorine, bromine, or iodine atom, a trifluoromethyl, C_{1-3}-alkyl, or C_{1-3}-alkoxy group,
where the heteroaryl groups referred to in the definition of the above remainders are a 5-member heteroaromatic group that contains an imino group, an oxygen or sulfur atom, or an imino group, an oxygen or sulfur atom, and one or two nitrogen atoms, or
a 6-member heteroaromatic group that contains one, two, or three nitrogen atoms,
where the 5-member heteroaromatic groups may each be substituted by one or two C_{1-3}-alkyl groups, and the 6-member heteroaromatic groups referred to above may each be substituted by one or two C_{1-3}-alkyl groups or by a fluorine, chlorine, bromine, or iodine atom, by a trifluoromethyl, hydroxy, or C_{1-3}-alkoxy group,
the isomers thereof and the salts thereof.

2. Compounds of the general formula I of claim 1, in which
R^1 means a hydrogen atom,
a C_{1-4}alkyl group,
a C_{1-4}-alkyl group substituted by an R_a group, where
R_a means a C_{3-6}-cycloalkyl or a phenyl group,
C_{2-4}-alkyl group terminally substituted by an R_b group, where
R_b, represents a hydroxy, C_{1-3}-alkoxy, amino, C_{1-3}-alkylamino, or di-(C_{1-3}-alkyl)-amino group,
or a C_{3-4}-alkenyl or C_{3-4}-alkinyl group, where the multiple bond is isolated from the ring nitrogen atom by at least one carbon atom,
R^2 means a hydrogen atom or a C_{1-3}-alkyl group,
R^3 means a linear C_{1-3}-alkyl group terminally substituted by the R_c group, where
R_c means a C_{5-6}-cycloalkenyl group,
a phenyl group optionally substituted by a fluorine, chlorine, or bromine atom, by a C_{1-3}-alkyl, or by a C_{1-3}-alkoxy group, or
a furanyl or thienyl group,
a linear or branched C_{3-6}-alkenyl group, in which the double bond is isolated from the ring nitrogen atom by at least one carbon atom,
or a linear or branched C_{3-6}-alkinyl group, in which the triple bond is isolated from the ring nitrogen atom by at least one carbon atom, and
R^4 means a pyrrolidine-1-yl group that in the 3-position is substituted by an amino, C_{1-3}-alkylamino, or di-(C_{1-3}-alkyl)-amino group,
a piperidine-1-yl or hexahydroazepine-1-yl group, that in the 3- or 4-position is substituted by an amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group,
a C_{5-7}-cycloalkyl group that in the 3-or 4-position is substituted by an amino, C_{1-3}-alkylamino, or di-(C_{1-3}-alkyl)-amino group,
a C_{1-3}-alkylamino group that is substituted at the nitrogen atom by a 2-aminoethyl group, or
a C_{5-7}-cycloalkylamino group that is substituted in the 2-position of the cycloalkyl part by an amino, C_{1-3}-alkylamino, or di-(C_{1-3}-alkyl)-amino group,
the isomers thereof and the salts thereof.

3. Compounds of the general formula I of claim 1, in which
R^1 means a hydrogen atom, a methyl, ethyl, propyl, 2-propyl, butyl, 2-methylpropyl, 2-propene-1-yl, 2-propyne- 1-yl, cyclopropylmethyl, benzyl, 2-phenylethyl, 3-phenylpropyl, 2-hydroxyethyl, 2-methoxyethyl, 2-(dimethylamino)ethyl, or 3-(dimethylamino)propyl group,
R^2 means a methyl group,
R^3 means a 2-butene-1-yl or 3-methyl-2-butene-1-yl group,
a 1-cyclopentene-1-ylmethyl group,
a 2-butyne-1-yl group,
a benzyl, 2-fluorobenzyl, or 3-fluorobenzyl group, or
a 2-thienylmethyl group, and
R^4 means a 3-aminopyrrolidine-1-yl group,
a 3-aminopiperidine-1-yl or 4-aminopiperidine-1-yl group,

a 3-aminohexahydroazepine-1-yl or 4-aminohexahydroazepine-1-yl group,
a 3-aminocyclohexyl group, N-(2-aminoethyl)-methylamino, or
a (2-aminocyclohexyl)amino group,
the isomers and salts thereof.

4. The following compounds of general formula I of claim 1:

(1) 1,3-dimethyl-7-benzyl-8-(3-aminopyrrolidine-1-yl)-xanthine,
(2) 1,3-dimethy1-7-(3-methyl-2-butene-1-yl)-8-(3-aminopyrrolidine-1-yl)-xanthine,
(3) 1,3-dimethyl-7-benzyl-8-(3-aminopiperidine-1-yl)-xanthine,
(4) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-[(trans-2-aminocyclohexyl)amino]-xanthine,
(5) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine,
(6) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-(4-aminopiperidine-1-yl)-xanthine,
(7) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-[(cis-2-aminocyclohexyl)amino]-xanthine,
(8) 1,3-dimethyl-7-(2-butyne-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine,
(9) 1,3-dimethyl-7-[(1-cyclopentene-1-yl)methyl]-8-(3-aminopiperidine-1-yl)-xanthine,
(10) 1,3-dimethyl-7-(2-thienylmethyl)-8-(3-aminopiperidine-1-yl)-xanthine,
(11) 1,3-dimethyl-7-(3-fluorobenzyl)-8-(3-aminopiperidine-1-yl)-xanthine,
(12) 1,3-dimethyl-7-(2-fluorobenzyl)-8-(3-aminopiperidine-1-yl)-xanthine,
(13) 1,3-dimethyl-7-(4-fluorobenzyl)-8-(3-aminopiperidine-1-yl)-xanthine,
(14) 1,3-dimethyl-7-(2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine,
(15) 1,3-bis-(cyclopropylmethyl)-7-benzyl-8-(3-aminopiperidine-1-yl)-xanthine,
(16) (R)-1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine,
(17) (S)-1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine,
(18) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminohexahydroazepine-1-yl)-xanthine,
(19) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-(4-aminohexahydroazepine-1-yl)-xanthine,
(20) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-(cis-3-aminocyclohexyl)-xanthine hydrochloride,
(21) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-(3-methylaminopiperidine-1-yl)-xanthine,
(22) 1-(2-phenylethyl)-3-methyl-7-(3-methyl-2-butene-1-yl)-8-(3-aminopiperidine-1-yl)-xanthine and
(23) 1,3-dimethyl-7-(3-methyl-2-butene-1-yl)-8-N-(2-aminoethyl)-methylamino]-xanthine

and the salts thereof.

5. Physiologically compatible salts of the compounds of at least one of claims 1 to 4 with inorganic or organic acids or bases.

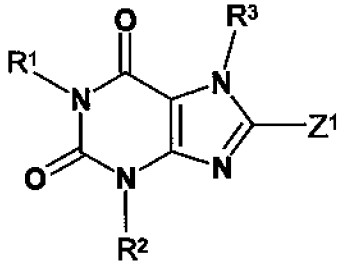
6. A medicinal product containing a compound of at least one of claims 1 to 4 or a physiologically compatible salt of claim 5 in addition to possibly one or more inert carriers and/or diluents.

7. The use of a compound of at least one of claims 1 to 5 to prepare a medicinal product that is suitable for treating diabetes mellitus type I and type II, arthritis, adipositas, allograft transplantation, and osteoporosis caused by calcitonin.

8. For the process to prepare the medicinal product of claim 6 wherein by nonchemical means a compound of at least one of claims 1 to 5 is incorporated into one or more inert carriers and/or diluents.

9. A process for preparing the compounds of general formula I of claims 1 to 5, wherein

a) to prepare compounds of general formula I, in which R^4 is one of the remainders recited in claim 1 by which a nitrogen atom is attached to the xanthine backbone
a compound of general formula



(III),

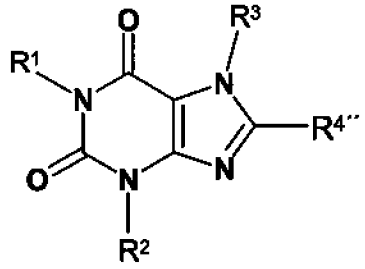
in which
R^1 to R^3 are defined as recited in claims 1 to 4, and
Z^1 represents a leaving group, such as a halogen atom, a substituted hydroxy, mercapto, sulfinyl, sulfonyl, or sulfonyloxy group, such as a chlorine or bromine atom, a methanesulfonyl or methanesulfonyloxy group, is reacted with a compound of the general formula

$H\text{-}R^{4'}$, (IV)

in which
$R^{4'}$ represents one of the remainders defined for R^4 in claims 1 to 4 that is attached by means of a nitrogen atom to the xanthine backbone of general formula I,

or

b) to prepare compounds of the general formula I, in which R^4 contains an amino group or an alkylamino group that is substituted in the alkyl part in accordance with the definition of claim 1, a compound of the general formula



(V),

in which R^1, R^2 and R^3 are defined as recited in claims 1 to 4, and

$R4^{11}$ contains an N-tert.-butyloxycarbonylamino group or an N-tert.-butyloxycarbonyl-N-alkylamino group, where the alkyl part of the N-tert.-butyloxycarbonyl-N-alkylamino group may be substituted as defined in claims 1 to 4,

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